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One-pot catalytic synthesis of 2,7-*bis*-substituted 4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes

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ABSTRACT

Catalytic methods for the synthesis of 2,7-*bis*-substituted 4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes have been developed. The structure was established on the basis of ^{1}H and ^{13}C NMR spectra, 2D NMR (HSQC, HMBC, COSY, NOESY) techniques, MALDI TOF/TOF spectra, and X-ray diffraction data. Primary screening of the synthesized hexaazaperhydropyrenes for antimicrobial activity was performed.

1. Introduction

Interest in the synthesis of annelated azapolycycles is generated by the possibility of their use as candidate compounds for the development of drugs with analgesic,[1] antibacterial[2] and antitumor[3,4] properties. The annelated azapolycycles include azaperhydropyrenes the synthesis of which was previously performed by the reaction of 1,4,5,8-tetraazadecalin with methyl acrylate,[5] or by the three-component cyclocondensation of primary amines with formaldehyde and 1,4,5,8-tetraazadecalin.[6] Recently,[7,8] effective methods for the synthesis of hexaazaperhydropyrenes have been developed by the intermolecular cyclization of *N,N-bis*(methoxymethyl)-N-alkylamines or by recyclization of 1,3,5-tricycloalkyl-1,3,5-triazines with 1,4,5,8-tetraazadecalin under the action of catalysts based on salts of *d*- and *f*-block elements.

2. Results and discussion

In continuation of our investigations[7–13] into the catalytic synthesis of different heterocycles, and also with the aim of developing an effective method for the synthesis of azapolycycles that are previously undescribed and promising for practical application, we have studied the possibility of the one-pot preparation of 2,7-*bis*-substituted hexaazaperhydropyrenes that bear methyl substituents directly attached to a polycyclic skeleton. Preliminary experiments have shown that the uncatalyzed interaction between the *in situ* prepared[14] *N,N-bis*(methoxymethyl)-*N*-propylamine and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins[15] (**1**) and (**2**) at 60 °C afforded the corresponding 2,7-dipropyl-4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhyd-ropyrenes (**3**) and (**4**) at a ratio of 1:1 in a total yield of no more than 40%. In our work we used racemic starting material (**1**) and (**2**) because it is very difficult to separate the 2,6- and 2,7-isomers. To increase the yield of the desired heterocycles (**3**) and (**4**), the reaction of *bis*(methoxymethyl)propylamine with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins was carried out under the action of catalysts based on transition and rare-earth metal salts which we have used previously in similar heterocyclization reactions.[7,9,10]

Among the catalysts tested, $SmCl_3 \cdot 6H_2O$ showed the highest activity in this reaction. In the presence of 5 mol% of $SmCl_3 \cdot 6H_2O$, 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins reacted with *N,N-bis*(methoxymethyl)-*N*-propylamine to produce 2,7-dipropyl-4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydro-pyrenes (**3**, **4**) at a ratio of ~1:1 in 81% total yield (Scheme 1). Similar results were obtained by replacing the *n*-propyl residue on the nitrogen atom by an *n*-Bu group. Intermolecular heterocyclization of 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins with *N,N-bis*(methoxymethyl)-N-alkylamines, prepared from linear primary alkyl amines, under

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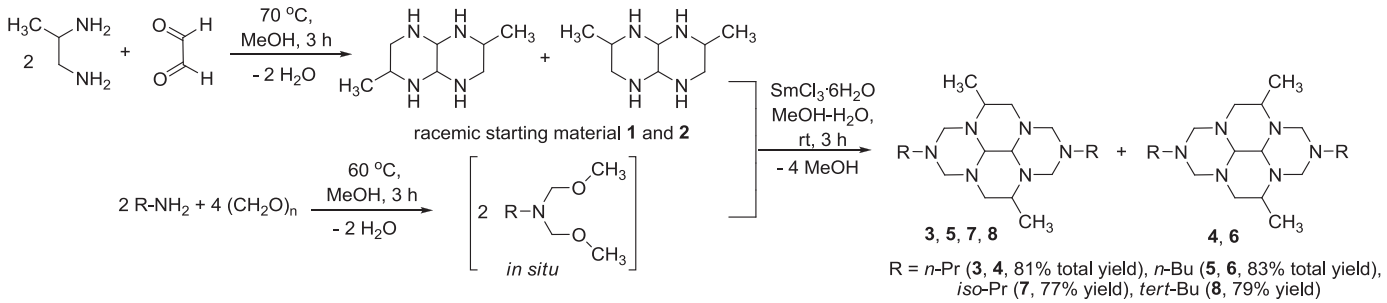


Scheme 1. Intermolecular heterocyclization of *N,N-bis*(methoxymethyl)-N-alkylamines with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins.

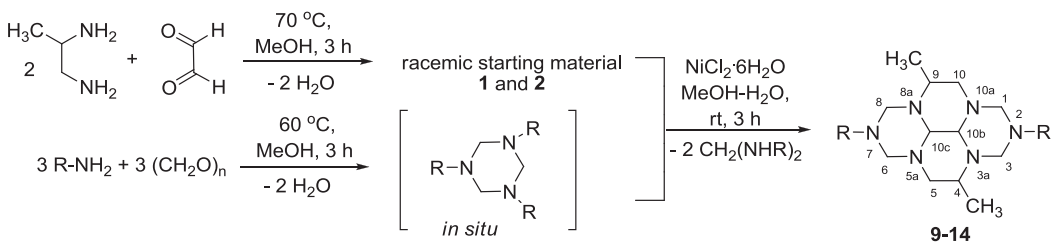
optimized reaction conditions (5 mol% $SmCl_3 \cdot 6H_2O$, MeOH–H_2O, 20 °C, 3 h) led to the formation of 2,7-dialkyl-4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaaza-perhydropyrenes (**3**, **4**) and (**5**, **6**) at a ratio of ~1:1 in 81–83% total yield according to Scheme 1. Because of their close polarity (R_f), we failed to satisfactorily separate hexaazaperhydropyrenes (**3**–**6**) using column chromatography. In the ^{13}C NMR spectra, compounds (**3**, **4**) and (**5**, **6**) gave two sets of signals corresponding to the isomeric mixture of 4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes. Diastereomeric products are readily identifiable in the ^{13}C NMR spectra. Thus, one signal at 82.7 ppm corresponds to carbon atoms of the symmetric 4,9-isomer at positions C-10b and C-10c. Due to the loss of molecular symmetry, carbon atoms of the 4,10-isomer at positions C-10b and C-10c resonate in the form of two signals at 82.2 and 83.2 ppm. Under the developed reaction conditions, branched amines (*iso*-$PrNH_2$, *tert*-$BuNH_2$) predominantly form 2,7-dialkyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes (**7**, **8**) in 77–79% yield (Scheme 1), while only trace amounts of 4,10-dimethyl derivatives were detected in the NMR spectra.

Based on our results[7] and the literature data,[16,17] it can be assumed that the catalytic cycle of the reaction between 2,6(7)-dimethyl-1,4,5,8-tetraazadecalines and *N,N-bis*(methoxymethyl)-N-alkylamine includes the step of coordinating the oxygen atom with the metal catalyst.[18] Subsequent nucleophilic addition of the nitrogen atom in tetraazadecalin to the iminium ion formed under the reaction conditions leads to intermolecular cyclization to give hexaazaperhydropyrenes.[7]

We have previously reported[8] that 1,3,5-tricycloalkyl-1,3,5-triazines can be used as efficient aminomethylation reagents in the synthesis of N-substituted hexaazaperhydropyrenes. In our subsequent experiments we investigated the possibility of the selective synthesis of 2,7-dicycloalkyl-substituted 4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes through the catalytic reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins. It has been shown that under the optimized reaction conditions (5 mol% $NiCl_2 \cdot 6H_2O$, MeOH–H_2O, 20°C, 3 h), 1,3,5-tricycloalkyl-1,3,5-triazines reacted with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins to selectively produce 2,7-dicycloalkyl-4,9-dimethyl-2,3a,5a,7,8a,10a hexaazaperhydropyrenes (**9**–**14**) in 79–92% yield (Scheme 2).

It should be noted that in the reaction of 1,3,5-tricyclopropyl-1,3,5-triazine with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins, along with 2,7-dicyclopropyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**9**) as the major isomer, we have observed the formation of the minor 4,10-isomer. The 3:1 (75:25) ratio of isomers was determined from the integration of four doublets in the region of 2.80–3.02 ppm which correspond to protons at positions C-1,6 and C-3,8. The possible mechanism[8] for the reaction between 1,3,5-tricycloalkyl-1,3,5-triazines and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins involves[16–18] several stages, namely, coordination of the triazine tertiary nitrogen atom with the metal catalyst, ring-opening of the triazine ring to produce an iminium ion, nucleophilic addition of the tetraazadecalin secondary nitrogen atom to the resulting carbocation, and subsequent cyclization with formation of the hexaazaperhydropyrene molecule.[8] The ^1H NMR spectra of compounds (**9**–**14**) contained two pairs of characteristic doublet signals with a geminal spin-spin coupling constant equal to 12 Hz, ascribed to the methylene protons of the carbon atoms, located between two nitrogen atoms, at positions H-1,6 and H-3,8 of the pyrene molecule. In the ^{13}C NMR spectra of compounds (**9**–**14**), there are five signals of equal intensity. Two of them, which appear in the region of 51.3–51.6 and 56.3–56.6 ppm, belong to carbon atoms at positions C-4,9 and C-5,10 of the dimethyl-substituted tetracyclic skeleton. Three other signals in the region 67.7–71.1, 71.1–74.4, and 82.5–82.8 ppm correspond to carbon atoms located between the nitrogen atoms at positions C-3,8, C-1,6 and C-10b,10c, respectively. The assignment of the signals was carried out based on two-dimensional homo- (COSY, NOESY) and heteronuclear (HSQC, HMBC) NMR experiments. Molecular peaks in the positive ion mode MALDI TOF/TOF mass spectra confirm the proposed structures.

Single crystals of compound (**9**) were obtained by slow



R = *cyclo*-C_3H_5 (**9**, 79% yield), *cyclo*-C_5H_9 (**10**, 81% yield), *cyclo*-C_6H_{11} (**11**, 92% yield), *cyclo*-C_7H_{13} (**12**, 83% yield), *cyclo*-C_8H_{15} (**13**, 87% yield), *norbornyl* (**14**, 79% yield)

Scheme 2. Cyclization of 1,3,5-tricycloalkyl-1,3,5-triazines with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins.

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evaporation from MeOH at room temperature. The obtained crystals belong to the triclinic crystal system. According to X-ray diffraction data (Fig. 1), the molecule of compound (**9**) has an inversion centre. The *trans*-hexaazaperhydropyrene skeleton is formed by two piperazine and two triazine rings, which adopt the *chair* conformation. The nitrogen atoms have a pyramidal conformation. The cyclopropane substituents occupy an axial position relative to the plane of the tetracyclic core and are in a *trans* configuration relative to each other.

Our further studies aimed at elucidating the possibility of the selective synthesis of 2,7-diadamantane-substituted hexaazaperhydropyrenes. Attempts to produce *N,N-bis*(methoxymethyl)-*N*-adamantylamines or 1,3,5-triadamantyl-1,3,5-triazines as the starting aminomethylation reagents were unsuccessful, possibly due to the bulky adamantyl substituent. We have developed a new approach to the synthesis of previously undescribed 2,7-diadamantyl-substituted 4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes through the one-pot catalytic condensation reaction between adamantylamines, formaldehyde, and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins. Among the catalysts tested in this reaction, the high-phase purity granular zeolite Y[19] in H form having a high crystallinity degree showed the greatest activity. We have found that one-pot multicomponent condensation between adamantylamines (adamantyl-1-amine, adamantyl-2-amine, rimantadine, 3,5-dimethyladamantyl-1-amine, 1-hydroxy-adamantyl-3-amine), formaldehyde, and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) occurs selectively under the developed reaction conditions (10 wt% zeolite Y, MeOH–H_2O, 20°C, 3 h) to afford 2,7-diadamantyl-substituted 4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes (**15**–**19**) in 50–67% yield (Scheme 3). Resonance assignments of the ^1H and ^{13}C NMR spectra for (**15**–**19**) were made by two-dimensional homo- (COSY, NOESY) and heteronuclear (HSQC, HMBC) NMR experiments. In the positive-ion mode, MALDI-TOF/TOF MS analysis successfully confirmed the proposed structures.

At the University of Queensland (Australia), a primary antimicrobial screening of the synthesized hexaazaperhydropyrenes has been performed for antifungal and antibacterial activity. Bacterial species like *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Cryptococcus neoformans* were used as test cultures. The results of biological tests have shown that 2,7-dicyclopentyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydro-pyrane (**10**) is active against fungi of the genus *Cryptococcus neoformans* var. *Grubii* (the inhibition value exceeds 80%) and is partially active against bacteria of the genus *Staphylococcus aureus* (the inhibition value ranges from 50.9% to 79.9%).

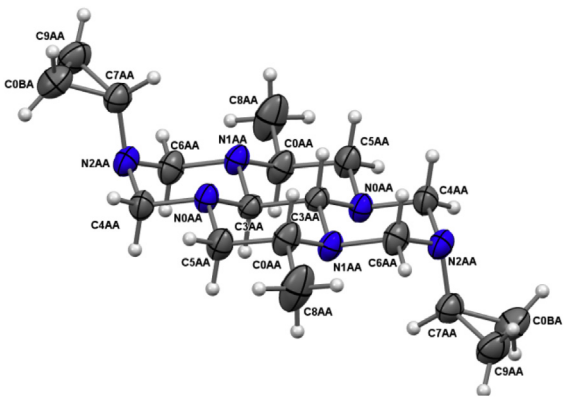


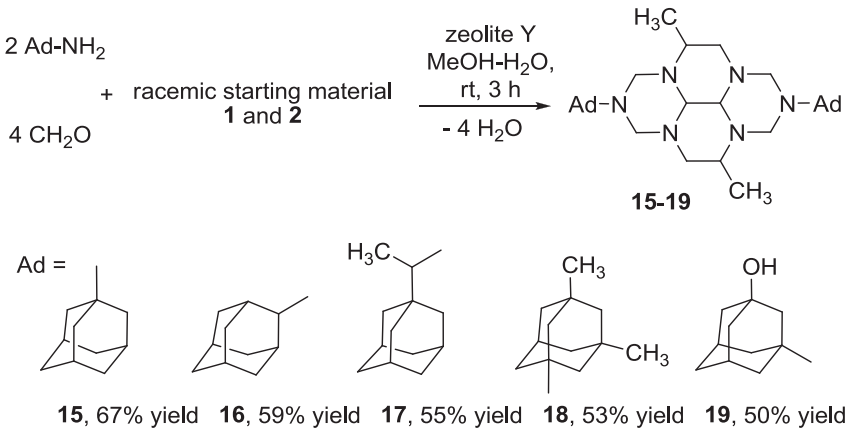
Fig. 1. The X-ray crystal structure of compound (**9**). Atoms are represented by thermal displacement ellipsoids (50% probability level).

3. Conclusions

Thus, we have developed a new one-pot catalytic method for the synthesis of promising 2,7-*bis*-substituted 4,9(10)-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes. These approaches include intermolecular heterocyclization of *N,N-bis*(methoxymethyl)-N-alkylamines, cyclization of 1,3,5-tricycloalkyl-1,3,5-triazines with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins under the action of catalysts based on salts of *d*- and *f*-block elements, and also the zeolite-catalyzed multicomponent condensation between adamantylamines, formaldehyde, and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins.

4. 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 ^1H 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



Scheme 3. Multicomponent condensation between adamantylamines, formaldehyde, and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins.

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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). 2,6(7)-Dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) were obtained as described previously.[15] X-ray diffraction analysis was performed on an automatic four-circle diffractometer XCalibur Eos (graphite monochromator, Mo*Kα* radiation, λ 0.71073 Å, *w*-scanning, 2θ max 62°). The data were acquired and processed with the aid of CrysAlisPro, version 1.171.36.20 (Oxford Diffraction Ltd.). The structure was solved by the direct method and refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized from the Fourier difference maps and were refined with fixed thermal and positional parameters. The calculations were performed using SHELX97.[20] The crystallographic data, coordinates of atoms, and geometric parameters for compound (**9**) were deposited at the Cambridge Crystallographic Data Centre (entry no. CCDC 1551102). The copies of the data are available free on demand from CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk) or through http://www.ccdc.cam.ac.uk/data_request/cif.

4.1. Heterocyclization of 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1, 2**) with N,N-bis(methoxymethyl)-N-alkylamines (General method)

A mixture of the corresponding *N,N-bis*(methoxymethyl)-N-alkylamine (2.00 mmol), obtained *in situ* by the reported procedure,[14] in MeOH (10 mL) with $SmCl_3 \cdot 6H_2O$ (0.018 g, 0.05 mmol) was stirred for 30 min at room temperature. Next, 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1, 2**) (0.17 g, 1.00 mmol) in H_2O (1 mL) were added to the mixture. The mixture was stirred at 20 °C for 3 h and evaporated. The residue was separated by column chromatography on silica gel (SiO_2) with MeOH as the eluent, and the heterocycles (**3**–**8**) were isolated. Compounds (**7**) and (**8**) were obtained as white powdered crystals (recrystallized from MeOH). The final products (**3**–**8**) were identified by spectral methods.

4.1.1. 2,7-Dipropyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**3**) and 2,7-dipropyl-4,10-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**4**)

Yield 0.27 g (81%), R_f (MeOH) 0.61; white powder, n_{max} (liquid film) 2956–2872 (br), 1457, 1211 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.90 (12H, t, *J* 8.5 Hz, CH_3, H-3′,3″), 0.99 (12H, br. s, CH_3, H-11,12), 1.47 (8H, q, *J* 9.5 Hz, CH_2, H-2′,2″), 1.94–2.04 (4H, m, CH_2, H_a-5,10 and H_a-5,9), 2.31 (1H, d, ^3J 9 Hz, CH, H-10c), 2.35–2.45 (4H, m, CH_2, H_b-5,10 and H_b-5,9; 4H, CH, H-4,9 and H-4,10; 2H, CH, H-10b,10c), 2.51 (1H, d, ^3J 9 Hz, CH, H-10b), 2.65–2.75 (8H, m, CH_2, H-1′,1″), 2.87 (4H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-3,8), 2.98 (4H, dd, $^2J_{ab}$ 12.5 and 12.5 Hz, CH_2, H_a-1,6), 3.60 (4H, dd, $^2J_{ba}$ 12.5 and 12.5 Hz, CH_2, H_b-1,6), 3.97 (4H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 11.8 (C-3′, C-3″), 16.7 and 17.0 (C-11, C-12), 21.4 (C-2′, C-2″), 51.3 and 51.4 (C-4, C-9 and C-4, C-10), 54.6 and 54.8 (C-1′, C-1″), 55.9 and 56.2 (C-5, C-10 and C-5, C-9), 70.6 and 70.8 (C-3, C-8), 74.1 and 74.2 (C-1, C-6), 82.2 (C-10b), 82.7 (C-10b, C-10c), 83.2 (C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 335 $[M-H]^+$ (100).

4.1.2. 2,7-Dibutyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**5**) and 2,7-dibutyl-4,10-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**6**)

Yield 0.30 g (83%), R_f (MeOH) 0.60; white powder, n_{max} (liquid film) 2955–2869 (br), 1460, 1214 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.89 (12H, t, *J* 9 Hz, CH_3, H-4′,4″), 0.98 (12H, br. s, CH_3, H-11,12), 1.31 (8H, q, *J* 9 Hz, CH_2, H-3′,3″), 1.40 (8H, q, *J* 9 Hz, CH_2, H-2′,2″), 1.92–1.99 (4H, m, CH_2, H_a-5,10 and H_a-5,9), 2.29 (1H, d, ^3J 9 Hz, CH, H-10c), 2.36–2.44 (4H, m, CH_2, H_b-5,10 and H_b-5,9; 4H, CH, H-4,9 and H-4,10; 2H, CH, H-10b,10c), 2.49 (1H, d, ^3J 9 Hz, CH, H-10b), 2.66–2.77 (8H, m, CH_2, H-1′,1″), 2.85 (4H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-3,8), 2.95 (4H, dd, $^2J_{ab}$ 12.5 and 12.5 Hz, CH_2, H_a-1,6), 3.58 (4H, dd, $^2J_{ba}$ 12.5 and 12.5 Hz, CH_2, H_b-1,6), 3.95 (4H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 14.0 (C-4′, C-4″), 16.7 and 17.0 (C-11, C-12), 20.4 (C-3′, C-3″), 30.4 (C-2′, C-2″), 51.2 and 51.4 (C-4, C-9 and C-4, C-10), 52.4 and 52.5 (C-1′, C-1″), 55.9 and 56.2 (C-5, C-10 and C-5, C-9), 70.6 and 70.8 (C-3, C-8), 74.0 and 74.2 (C-1, C-6), 82.2 (C-10b), 82.7 (C-10b, C-10c), 83.1 (C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 363 $[M-H]^+$ (100).

4.1.3. 2,7-Diisopropyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**7**)

Yield 0.26 g (77%), R_f (MeOH) 0.63, white powdered crystals, mp 184–186 °C; n_{max} (liquid film) 2965–2875 (br), 1464, 1214 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.01 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 1.10 (12H, d, *J* 8 Hz, CH_3, H-2′,2″,3′,3″), 1.99 (2H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-5,10), 2.38–2.48 (2H, m, CH_2, H_b-5,10; 4H, CH, H-4,9,10b,10c), 2.86 (2H, d, $^2J_{ab}$ 12.5 Hz, CH_2, H_a-3,8), 2.94 (2H, d, $^2J_{ab}$ 12.5 Hz, CH_2, H_a-1,6), 3.17–3.26 (2H, m, CH, H-1′,1″), 3.78 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-1,6), 4.17 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.6 (C-11, C-12), 20.5 and 20.9 (C-2′, C-2″, C-3′, C-3″), 48.9 (C-1′, C-1″), 51.4 (C-4, C-9), 56.5 (C-5, C-10), 68.1 (C-3, C-8), 71.4 (C-1, C-6), 82.2 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 335 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{18}H_{36}N_6$: C, 64.24; H, 10.78; N, 24.97; found: C, 64.19; H, 10.75; N, 24.92.

4.1.4. 2,7-Ditertbutyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**8**)

Yield 0.29 g (79%), R_f (MeOH) 0.64, white powdered crystals, mp 185–187 °C; n_{max} (liquid film) 2952–2866 (br), 1463, 1261 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.03 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 1.13 (18H, br. s, CH_3, H-2′,2″,3′,3″,4′,4″), 2.05 (2H, t, CH_2, $^2J_{ab}$ 13 Hz, H_a-5,10), 2.36 (2H, br. s, CH, H-10b,10c), 2.42–2.55 (2H, m, CH_2, H_b-5,10; 2H, CH, H-4,9), 2.58 (2H, d, $^2J_{ab}$ 10.5 Hz, CH_2, H_a-3,8), 2.69 (2H, d, $^2J_{ab}$ 10.5 Hz, CH_2, H_a-1,6), 3.86 (2H, d, $^2J_{ba}$ 10.5 Hz, CH_2, H_b-1,6), 4.26 (2H, d, $^2J_{ba}$ 10.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.7 (C-11, C-12), 27.0 (C-2′, C-2″, C-3′, C-3″, C-4′, C-4″), 51.9 (C-4, C-9), 52.9 (C-1′, C-1″), 57.0 (C-5, C-10), 66.4 (C-3, C-8), 69.8 (C-1, C-6), 82.4 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 403 $[M+K]^+$ (90), 387 $[M+Na]^+$ (80), 363 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{20}H_{40}N_6$: C, 65.89; H, 11.06; N, 23.05; found: C, 65.82; H, 11.02; N, 23.00.

4.2. Ring transformation reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) (General method)

A round bottom flask equipped with a magnetic stir bar was charged with MeOH (10 mL), the corresponding 1,3,5-tricycloalkyl-1,3,5-triazine (2.00 mmol), obtained *in situ* by the reported procedure[8] and $NiCl_2 \cdot 6H_2O$ (0.012 g, 0.05 mmol). The mixture was stirred at room temperature for 30 min. Next, 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) (0.17 g, 1.00 mmol) in H_2O (1 mL) were added to the mixture. The mixture was stirred at 20 °C for 3 h and evaporated. The residue was separated by column chromatography on silica gel (SiO_2) with MeOH as the eluent. Compound

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(**9**) was obtained as colorless crystals (recrystallized from MeOH). Compounds (**10**–**14**) were obtained as white powdered crystals. The final products (**9**–**14**) were identified by spectral methods.

4.2.1. 2,7-Dicyclopropyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**9**)

Yield 0.26 g (79%), R_f (MeOH) 0.61, colorless crystals in the form of prisms, mp 180–182 °C; n_{max} (liquid film) 2990–2875 (br), 1450, 1215 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.42–0.48 (8H, m, CH_2, H-2′,2″,3′,3″), 1.03 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 2.02 (2H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-5,10), 2.38–2.58 (2H, m, CH_2, H_b-5,10; 6H, CH, H-1′,1″,4,9,10b,10c), 2.89 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-3,8), 2.95 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-1,6), 3.72 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-1,6), 4.07 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 6.4 and 6.5 (C-2′, C-2″, C-3′, C-3″), 16.7 (C-11, C-12), 33.3 (C-1′, C-1″), 51.6 (C-4, C-9), 56.3 (C-5, C-10), 71.1 (C-3, C-8), 74.4 (C-1, C-6), 82.6 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 333 $[M+H]^+$ (100). Anal. Calcd. (%) for $C_{18}H_{32}N_6$: C, 65.02; H, 9.70; N, 25.28; found: C, 64.97; H, 9.67; N, 25.22. Crystal data for (**9**): $C_{18}H_{32}N_6$, M = 332.50, triclinic, P-1, a = 7.324 (2) Å, b = 8.805 (2) Å, c = 8.952 (3) Å, α = 61.94 (3), β = 68.16 (3), γ = 87.28 (2), V = 467.1 (2) Å^3, T = 298 (2)K, D_{calcd} = 1.182 g/cm^3, Z = 1, reflection collected = 3379, independent reflection = 2093 (R_{int} = 0.0135), R values [$I > 2\sigma(I)$, 1332 reflection]: R_1 = 0.0477, wR_2 = 0.1598, S = 0.900; CCDC 1551102.

4.2.2. 2,7-Dicyclopentyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**10**)

Yield 0.31 g (81%), R_f (MeOH) 0.63, white powdered crystals, mp 228–230 °C; n_{max} (liquid film) 2955–2858 (br), 1459, 1209 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.01 (6H, d, *J* 7 Hz, CH_3, H-11,12), 1.30–1.40 (4H, m, CH_2, H_a-2′,2″,5′,5″), 1.54–1.62 (4H, m, CH_2, H_a-3′,3″,4′,4″), 1.65–1.73 (4H, m, CH_2, H_b-3′,3″,4′,4″), 1.85–1.92 (4H, m, CH_2, H_b-2′,2″,5′,5″), 1.97 (2H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-5,10), 2.35–2.48 (2H, m, CH_2, H_b-5,10; 4H, CH, H-4,9,10b,10c), 2.86 (2H, d, $^2J_{ab}$ 12.5 Hz, CH_2, H_a-3,8), 2.94 (2H, d, $^2J_{ab}$ 12.5 Hz, CH_2, H_a-1,6), 3.32–3.36 (2H, m, CH, H-1′,1″), 3.72 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-1,6), 4.11 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.7 (C-11, C-12), 23.9 and 24.0 (C-3′, C-3″, C-4′, C-4″), 31.2 (C-2′, C-2″, C-5′, C-5″), 51.3 (C-4, C-9), 56.4 (C-5, C-10), 60.0 (C-1′, C-1″), 69.8 (C-3, C-8), 73.4 (C-1, C-6), 82.6 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 387 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{22}H_{40}N_6$: C, 68.00; H, 10.38; N, 21.62; found: C, 67.93; H, 10.33; N, 21.57.

4.2.3. 2,7-Dicyclohexyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**11**)

Yield 0.38 g (92%), R_f (MeOH) 0.63, white powdered crystals, mp 238–240 °C; n_{max} (liquid film) 2922–2859 (br), 1444, 1214 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.02 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 1.08–1.18 (6H, m, CH_2, H_a-2′,2″,4′,4″,6′,6″), 1.24–1.34 (4H, m, CH_2, H_a-3′,3″,5′,5″), 1.62 (2H, br. s, CH_2, H_b-4′,4″), 1.72–1.80 (4H, m, CH_2, H_b-3′,3″,5′,5″), 1.93–2.03 (6H, m, CH_2, H_a-5,10; H_b-2′,2″,6′,6″), 2.36–2.48 (2H, m, CH_2, H_b-5,10; 4H, CH, H-4,9,10b,10c), 2.80–2.86 (2H, m, CH, H-1′,1″), 2.88 (2H, d, $^2J_{ab}$ 12.5 Hz, CH_2, H_a-3,8), 2.96 (2H, d, $^2J_{ab}$ 12.5 Hz, CH, H_a-1,6), 3.80 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-1,6), 4.19 (2H, d, $^2J_{ba}$ 12.5 Hz, CH_2, H_b-3,6); δ_C (125.78 MHz, $CDCl_3$) 16.7 (C-11, C-12), 25.3 and 25.3 (C-3′, C-3″, C-5′, C-5″), 26.0 (C-4′, C-4″), 30.5 и 30.9 (C-2′, C-2″, C-6′, C-6″), 51.4 (C-4, C-9), 56.4 (C-5, C-10), 57.0 (C-1′, C-1″), 67.7 (C-3, C-8), 71.1 (C-1, C-6), 82.8 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 415 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{24}H_{44}N_6$: C, 69.18; H, 10.64; N, 20.18; found: C, 69.11; H, 10.60; N, 20.12.

4.2.4. 2,7-Dicycloheptyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**12**)

Yield 0.37 g (83%), R_f (MeOH) 0.60, white powdered crystals, mp 187–189 °C; n_{max} (liquid film) 2921–2852 (br), 1451, 1202 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.01 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 1.35–1.45 (4H, m, CH_2, H_a-3′,3″,6′,6″), 1.47–1.57 (12H, m, CH_2, H-4′,4″,5′,5″; H_a-2′,2″,7′,7″), 1.59–1.69 (4H, m, CH_2, H_b-3′,3″,6′,6″), 1.80–1.90 (4H, m, CH_2, H_b-2′,2″,7′,7″), 2.00 (2H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-5,10), 2.37 (2H, br. s, CH, H_b-10b,10c), 2.39–2.49 (2H, m, CH, H-4,9; 2H, CH_2, H_b-5,10), 2.81 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-3,8), 2.88 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-1,6), 2.91–2.98 (2H, m, CH, H-1′,1″), 3.70 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-1,6), 4.07 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.7 (C-11, C-12), 24.7 and 24.8 (C-3′, C-3″, C-6′, C-6″), 28.4 (C-4′, C-4″, C-5′, C-5″), 31.0 and 31.5 (C-2′, C-2″, C-7′, C-7″), 51.6 (C-4, C-9), 56.6 (C-5, C-10), 60.1 (C-1′, C-1″), 68.4 (C-3, C-8), 71.5 (C-1, C-6), 82.6 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 443 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{26}H_{48}N_6$: C, 70.22; H, 10.88; N, 18.90; found: C, 70.16; H, 10.82; N, 18.81.

4.2.5. 2,7-Dicyclooctyl-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**13**)

Yield 0.41 g (87%), R_f (MeOH) 0.61, white powdered crystals, mp 169–171 °C; n_{max} (liquid film) 2920–2848 (br), 1468, 1214 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.01 (6H, d, *J* 7.5 Hz, CH_3, H-11,12), 1.40–1.60 (20H, m, CH_2, H_a-2′,2″,3′,3″,7′,7″,8′,8″; H-4′,4″,5′,5″,6′,6″), 1.65–1.75 (4H, m, CH_2, H_b-3′,3″,7′,7″), 1.78–1.88 (4H, m, CH_2, H_b-2′,2″,8′,8″), 1.99 (2H, t, $^2J_{ab}$ 13 Hz, CH_2, H_a-5,10), 2.37 (2H, br. s, CH, H-10b,10c), 2.40–2.50 (2H, m, CH_2, H_b-5,10; 2H, CH, H-4,9), 2.81 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-3,8), 2.88 (2H, d, $^2J_{ab}$ 12 Hz, CH_2, H_a-1,6), 2.95–3.05 (2H, m, CH, H-1′,1″), 3.71 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-1,6), 4.09 (2H, d, $^2J_{ba}$ 12 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.7 (C-11, C-12), 24.4 (C-3′, C-3″, C-7′, C-7″), 26.1 (C-5′, C-5″), 27.2 and 27.3 (C-4′, C-4″, C-6′, C-6″), 29.0 and 29.3 (C-2′, C-2″, C-8′, C-8″) 51.5 (C-4, C-9), 56.6 (C-5, C-10), 58.3 (C-1′, C-1″), 68.4 (C-3, C-8), 71.6 (C-1, C-6), 82.7 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 511 $[M+K]^+$ (100), 495 $[M+Na]^+$ (50), 471 $[M-H]^+$ (10). Anal. Calcd. (%) for $C_{28}H_{52}N_6$: C, 71.14; H, 11.09; N, 17.77; found: C, 71.08; H, 11.02; N, 17.72.

4.2.6. 2,7-Dibicyclo[2.2.1]hept-2-yl-4,9-dimethyl-2,3a,5a,7,-8a,10a-hexaazaperhydropyrene (**14**)

Yield 0.35 g (79%), R_f (MeOH) 0.67, white powdered crystals, mp 239–241 °C; n_{max} (liquid film) 2953–2869 (br), 1450, 1214 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.95–1.12 (6H, m, CH_3, H-11,12; 6H, CH_2, H_a-3′,3″,6′,6″,7′,7″), 1.30–1.55 (10H, m, CH_2, H_b-3′,3″,6′,6″,7′,7″; H-5′,5″), 1.92–2.04 (2H, m, CH_2, H_a-5,10), 2.24 (2H, br. s, CH, H-4′,4″), 2.30 (2H, br. s, CH, H-2′,2″), 2.60–2.78 (2H, m, CH_2, H_b-5,10; 4H, CH, H-4,9,10b,10c), 2.70–2.82 (2H, m, CH, H-1′,1″; 4H, CH_2, H_a-1,3,6,8), 3.70–3.82 (2H, m, CH_2, H_b-1,6), 4.12–4.20 (2H, m, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.8 (C-11, C-12), 27.6 (C-6′, C-6″), 28.4 (C-7′, C-7″), 35.2 (C-3′, C-3″), 36.3 (C-4′, C-4″) 37.4 (C-5′, C-5″), 38.4 (C-2′, C-2″), 51.5 (C-4′, C-9), 56.5 (C-5, C-10), 62.5 (C-1′, C-1″) 68.8 (C-3, C-8), 72.6 (C-1, C-6), 82.5 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 439 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{26}H_{44}N_6$: C, 70.86; H, 10.06; N, 19.08; found: C, 70.77; H, 10.01; N, 19.02.

4.3. Multicomponent condensation of adamantylamines with formaldehyde and 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) (General method)

A round bottom flask equipped with a magnetic stir bar was charged with MeOH (10 mL), the corresponding adamantylamine (2.00 mmol), formaldehyde (0.45 mL, 4.00 mmol) and zeolite Y[20] (10 wt%). Next, 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (**1**, **2**) (0.17 g, 1.00 mmol) in H_2O (1 mL) were added to the mixture. The mixture was stirred at 20 °C for 3 h. The white precipitate was filtered and washed twice with MeOH (5 mL). Compounds (**15**–**19**) were obtained as white powdered crystals (recrystallized from $CHCl_3$). The final products (**15**–**19**) were identified by spectral

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methods.

4.3.1. 2,7-Di(1-adamantyl)-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**15**)

Yield 0.35 g (67%), R_f ($CHCl_3$) 0.75, white powdered crystals, mp 250–252 °C; n_{max} (liquid film) 2922–2852 (br), 1457, 1216 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.03 (6H, d, *J* 6 Hz, CH_3, H-11,12), 1.59–1.67 (12H, m, CH_2, H-4′,4″,9′,9″,10′,10″), 1.79 (12H, br. s, CH_2, H-2′,2″,6′,6″,7′,7″), 2.01 (2H, t, $^2J_{ab}$ 11 Hz, CH_2, H_a-5,10), 2.07 (6H, br. s, CH, H-3′,3″,5′,5″,8′,8″), 2.35 (2H, br. s, CH, H-10b,10c), 2.38–2.45 (2H, m, CH, H-4,9), 2.48–2.51 (2H, m, CH, H_b-5,10), 2.69 (2H, d, $^2J_{ab}$ 9 Hz, CH_2, H_a-3,8), 2.80 (2H, d, $^2J_{ab}$ 9 Hz, CH_2, H_a-1,6), 3.93 (2H, d, $^2J_{ba}$ 9 Hz, CH_2, H_b-1,6), 4.34 (2H, d, $^2J_{ba}$ 9 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.8 (C-11, C-12), 29.6 (C-3′, C-3″, C-5′, C-5″, C-8′, C-8″), 36.8 (C-4′, C-4″, C-9′, C-9″, C-10′, C-10″), 40.0 (C-2′, C-2″, C-6′, C-6″, C-7′, C-7″), 51.9 (C-4, C-9) 53.5 (C-1′, C-1″), 57.0 (C-5, C-10), 65.1 (C-3, C-8), 68.5 (C-1, C-6), 82.8 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 559 $[M+K]^+$ (40), 543 $[M+Na]^+$ (100), 519 $[M-H]^+$ (60). Anal. Calcd. (%) for $C_{32}H_{52}N_6$: C, 73.80; H, 10.06; N, 16.14; found: C, 73.74; H, 10.02; N, 16.09.

4.3.2. 2,7-Di(2-adamantyl)-4,9-dimethyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrene (**16**)

Yield 0.31 g (59%), R_f ($CHCl_3$) 0.73, white powdered crystals, mp 249–251 °C; n_{max} (liquid film) 2923–2853 (br), 1461, 1211 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.99 (6H, d, *J* 6 Hz, CH_3, H-11,12), 1.41 (4H, d, *J* 11 Hz, CH_2, H_a-7′,7″,9′,9″), 1.68–1.88 (12H, m, CH_2, H-3′,3″,5′,5″,10′,10″; 4H, CH, H-4′,4″,8′,8″), 1.92–2.08 (6H, m, CH_2, H_b-7′,7″,9′,9″; H_a-5,10; 4H, CH, H-2′,2″,6′,6″), 2.43 (2H, br. s, CH_2, H_b-5,10; 4H, CH, H-4,9,10b,10c), 2.82 (2H, d, $^2J_{ab}$ 10 Hz, CH_2, H_a-3,8), 2.89 (2H, d, $^2J_{ab}$ 10 Hz, CH_2, H_a-1,6), 3.08 (2H, br. s, CH, H-1′,1″), 3.80 (2H, d, $^2J_{ba}$ 10 Hz, CH_2, H_b-1,6), 4.20 (2H, d, $^2J_{ba}$ 10 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.8 (C-11, C-12), 27.3 and 27.6 (C-4′, C-4″, C-8′, C-8″), 28.9 (C-2′, C-2″, C-6′, C-6″), 31.2 and 31.2 (C-7′, C-7″, C-9′, C-9″), 37.1 and 37.1 (C-3′, C-3″, C-5′, C-5″), 37.9 (C-10′, C-10″), 51.3 (C-4, C-9) 56.4 (C-5, C-10), 60.2 (C-1′, C-1″), 67.2 (C-3, C-8), 70.8 (C-1, C-6), 82.9 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 559 $[M+K]^+$ (40), 543 $[M+Na]^+$ (30), 519 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{32}H_{52}N_6$: C, 73.80; H, 10.06; N, 16.14; found: C, 73.73; H, 10.00; N, 16.10.

4.3.3. 2,7-Bis[1-(1-adamantyl)ethyl]-4,9-dimethyl-2,3a,5a,7,-8a,10a-hexaazaperhydropyrene (**17**)

Yield 0.32 g (55%), R_f ($CHCl_3$) 0.76, white powdered crystals, mp 254–256 °C; n_{max} (liquid film) 2919–2850 (br), 1451, 1215 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.97 (6H, br. s, CH_3, H-11,12), 1.22 and 1.28 (6H, d, *J* 5.6 Hz, CH_3, H-12′,12″), 1.42 (6H, d, *J* 9.2 Hz, CH_2, H_a-3′,3″,7′,7″,8′,8″), 1.55–1.68 (18H, m, CH_2, H_b-3′,3″,7′,7″,8′,8″; H-5′,5″,10′,10″,11′,11″), 1.81–1.88 (2H, m, CH_2, H_a-5,10), 1.94 (6H, br. s, CH, H-4′,4″,6′,6″,9′,9″), 2.25–2.45 (2H, m, CH_2, H_b-5,10; 6H, CH, H-1′,1″,4,9,10b,10c), 2.98–3.08 (3H, m, CH_2, H_a-1,3,8), 3.16–3.20 (1H, m, CH_2, H_a-6), 3.43–3.49 (2H, m, CH_2, H_b-1,6), 3.80 (1H, d, $^2J_{ba}$ 8 Hz, CH_2, H_b-3), 3.89 (1H, d, $^2J_{ba}$ 8 Hz, CH_2, H_b-8); δ_C (125.78 MHz, $CDCl_3$) 10.3 and 10.8 (C-12′, C-12″), 16.5 and 16.8 (C-11, C-12), 28.6 (C-4′, C-4″, C-6′, C-6″, C-9′, C-9″), 37.4 (C-5′, C-5″, C-10′, C-10″, C-11′, C-11″), 38.4 and 38.4 (C-2′, C-2″), 38.6 and 38.7 (C-3′, C-3″, C-7′, C-7″, C-8′, C-8″), 51.1 and 51.5 (C-4, C-9), 55.7 and 56.3 (C-5, C-10), 66.7 and 67.0 (C-1′, C-1″), 67.4 and 74.3 (C-3, C-8), 71.2 and 77.3 (C-1, C-6), 83.1 and 83.3 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 615 $[M+K]^+$ (50), 599 $[M+Na]^+$ (40), 575 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{36}H_{60}N_6$: C, 74.95; H, 10.48; N, 14.57; found: C, 74.89; H, 10.44; N, 14.51.

4.3.4. 2,7-Bis(3,5-dimethyl-1-adamantyl)-4,9-dimethyl-2,3a,5a,-7,8a,10a-hexaazaperhydropyrene (**18**)

Yield 0.31 g (53%), R_f ($CHCl_3$) 0.76, white powdered crystals, mp 255–257 °C; n_{max} (liquid film) 2923–2853 (br), 1455, 1207 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 0.85 (12H, br. s, CH_3, H-11′,11″,12′,12″), 1.05 (6H, d, *J* 6 Hz, CH_3, H-11,12), 1.08–1.14 (4H, m, CH_2, H-9′,9″), 1.28 (8H, br. s, CH_2, H-4′,4″,10′,10″), 1.34–1.45 (8H, m, CH_2, H-6′,6″,7′,7″), 1.64 (4H, br. s, CH_2, H-2′,2″), 2.04 (2H, t, $^2J_{ab}$ 10 Hz, CH_2, H_a-5,10), 2.14 (2H, br. s, CH, H-3′,3″), 2.35 (2H, br. s, CH, H-10b,10c), 2.42–2.48 (2H, m, CH, H-4,9), 2.50–2.53 (2H, m, CH_2, H_b-5,10), 2.67 (2H, d, $^2J_{ab}$ 8.5 Hz, CH_2, H_a-3,8), 2.77 (2H, d, $^2J_{ab}$ 8.5 Hz, CH_2, H_a-1,6), 3.93 (2H, d, $^2J_{ba}$ 8.5 Hz, CH_2, H_b-1,6), 4.32 (2H, d, $^2J_{ba}$ 8.5 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 16.8 (C-11, C-12), 30.3 (C-3′, C-3″), 30.6 (C-11′, C-11″, C-12′, C-12″), 32.3 (C-5′, C-5″, C-8′, C-8″), 38.3 (C-2′, C-2″), 43.0 (C-4′, C-4″, C-10′, C-10″), 45.8 and 45.9 (C-6′, C-6″, C-7′, C-7″), 50.9 (C-9′, C-9″), 51.9 (C-4, C-9) 55.3 (C-1′, C-1″), 57.0 (C-5, C-10), 65.4 (C-3, C-8), 68.8 (C-1, C-6), 82.7 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 575 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{36}H_{60}N_6$: C, 74.95; H, 10.48; N, 14.57; found: C, 74.87; H, 10.45; N, 14.50.

4.3.5. 2,7-Bis(1-hydroxy-1-adamantyl)-4,9-dimethyl-2,3a,5a,-7,8a,10a-hexaazaperhydropyrene (**19**)

Yield 0.28 g (50%), R_f ($CHCl_3$) 0.69, white powdered crystals, mp 246–248 °C; n_{max} (liquid film) 2922–2854 (br), 1461, 1223 cm^{-1}; δ_H (500.17 MHz, $CDCl_3$) 1.03 (6H, d, *J* 6 Hz, CH_3, H-11,12), 1.50 (4H, br. s, CH_2, H-10′,10″), 1.65 (8H, br. s, CH_2, H-4′,4″,9′,9″), 1.68–1.80 (12H, m, CH_2, H-2′,2″,6′,6″,7′,7″), 1.99 (2H, t, $^2J_{ab}$ 10.5 Hz, CH_2, H_a-5,10), 2.27 (6H, br. s, CH, H-5′,5″,8′,8″,10b,10c), 2.37–2.43 (2H, m, CH, H-4,9), 2.46 (2H, t, $^2J_{ba}$ 10.5 Hz, CH_2, H_b-5,10), 2.75 (2H, d, $^2J_{ab}$ 9 Hz, CH_2, H_a-3,8), 2.82 (2H, d, $^2J_{ab}$ 9 Hz, CH_2, H_a-1,6), 3.92 (2H, d, $^2J_{ba}$ 9 Hz, CH_2, H_b-1,6), 4.32 (2H, d, $^2J_{ba}$ 9 Hz, CH_2, H_b-3,8); δ_C (125.78 MHz, $CDCl_3$) 17.0 (C-11, C-12), 30.8 (C-5′, C-5″, C-8′, C-8″), 35.2 (C-10′, C-10″), 38.9 (C-6′, C-6″, C-7′, C-7″), 44.4 (C-4′, C-4″, C-9′, C-9″), 48.0 (C-2′, C-2″), 52.0 (C-4, C-9), 56.5 (C-5, C-10), 57.1 (C-1′, C-1″), 65.3 (C-3, C-8), 68.6 (C-1, C-6), 69.9 (C-3′, C-3″), 83.1 (C-10b, C-10c); MALDI TOF/TOF: *m/z* (I_{rel}, %): 551 $[M-H]^+$ (100). Anal. Calcd. (%) for $C_{32}H_{52}N_6O_2$: C, 69.53; H, 9.48; N, 15.20; O, 5.79; found: C, 69.48; H, 9.43; N, 15.14.

5. Biological screening

5.1. Sample preparation

Samples were provided by the collaborator and stored frozen at −20 °C. Samples were prepared in DMSO and water to a final testing concentration of 32 μg/mL or 20 μM (unless otherwise indicated in the data sheet), in 384-well, non-binding surface plate (NBS) for each bacterial/fungal strain, and in duplicate (n = 2), and keeping the final DMSO concentration to a maximum of 1% DMSO. All the sample-preparation where done using liquid handling robots. Compounds that showed solubility issues during stock solution preparation are detailed in the data sheet.

5.2. Antimicrobial assay

5.2.1. Procedure

All bacteria were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5–3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then added to each well of the compound containing plates, giving a cell density of $5_{\times}105$ CFU/mL and a total volume of 50 μL. All the plates were covered and incubated at 37 °C for 18 h without shaking.

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5.2.2. Analysis

Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD_{600}), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The significance of the inhibition values was determined by modified Z-scores, calculated using the median and MAD of the samples (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as actives. Samples with inhibition values between 50 and 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as partial actives.

5.3. Antifungal assay

5.3.1. Procedure

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1×10^6 to 5×10^6 CFU/mL (as determined by OD_{530}) was prepared from five colonies. The suspension was subsequently diluted and added to each well of the compound-containing plates giving a final cell density of fungi suspension of 2.5×10^3 CFU/mL and a total volume of 50 μL. All plates were covered and incubated at 35 °C for 24 h without shaking.

5.3.2. Analysis

Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD_{530}), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm ($OD_{600\text{-}570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate. The significance of the inhibition values was determined by modified Z-scores, calculated using the median and MAD of the samples (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as actives. Samples with inhibition values between 50 and 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as partial actives.

5.4. Antibiotic standards preparation and quality control

Colistin and Vancomycin were used as positive bacterial inhibitor standards for Gram-negative and Gram-positive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for *C. albicans and C. neoformans.* The antibiotics were provided in 4 concentrations, with 2 above and 2 below its MIC value, and plated into the first 8 wells of column 23 of the 384-well NBS plates. The quality control (QC) of the assays was determined by the antimicrobial controls and the Z′-factor (using positive and negative controls). Each plate was deemed to fulfil the quality criteria (pass QC), if the Z′-factor was above 0.4, and the antimicrobial standards showed full range of activity, with full growth inhibition at their highest concentration, and no growth inhibition at their lowest concentration.

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