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Pd(0)–Catalyzed Amination in the Synthesis of Bicyclic Compounds Comprising Triazacycloalkane and Fluorophore Moieties

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Direct introduction of one dansyl fluorophore group into the molecule of 1,4,7-triazacyclononane (TACN) and 1,5,9-triazacyclododecane (TACD) was shown to be possible followed by the modification of triazacycles with two bromobenzyl substituents. The resulting compounds were used in the Pd(0)-catalyzed macrocyclization reaction with 1,13-diaza-4,7,10-trioxatridecane to provide corresponding cryptands. The synthesis of bicyclic derivatives of TACN bearing naphthyl and acridinyl fluorophore groups was accomplished via an alternative procedure using aminal-protected TACN. The possibility to form tetracyclic compounds starting from N,N',N''-tris(3-bromobenzyl) substituted TACN was demonstrated. Three cryptands bearing dansyl fluorophore were tested as potential fluorescent chemosensors for metal cations and were found to act as molecular fluorescent probes for Cu(II) and Al(III) by total emission quenching in the presence of these cations.

Keywords: Pd Catalysis, triazacycles, amination, cryptands, fluorescence.

Pd(0)–Катализируемое аминирование в синтезе бициклических соединений, содержащих триазациклоалкановые и флуорофорные фрагменты

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Показана возможность прямого введения одной дансильной флуорофорной группы в молекулу 1,4,7-триазациклононана (ТАЦН) и 1,5,9-триазациклододекана (ТАЦД) с последующей модификацией триазациклов двумя бромбензильными заместителями. Полученные соединения использованы в Pd(0)-катализируемой макроциклизации с 1,13-диаза-4,7,10-триоксатридеканом с образованием соответствующих криптандов. С использованием альтернативного подхода через ТАЦН с аминальной защитой были синтезированы бициклы, содержащие нафтильный и акридинильный флуорофоры. Продемонстрирована возможность получения тетрациклических соединений различного строения исходя из N,N',N''-трис(3-бромбензил) замещенного ТАЦН. Три криптанда исследованы в качестве флуоресцентных детекторов катионов металлов и показана их возможность выступать в качестве молекулярных проб на катионы Cu(II) и Al(III) за счет полного тушения флуоресценции в присутствии данных металлов.

Ключевые слова: Pd Катализ, триазациклы, аминирование, криптанды, флуоресценция.

Introduction

One of the important tasks of the modern organic chemistry is the search for new chemosensors able of selective detection of metal cations. Chemosensors exploiting fluorescence for producing analytical response possess many favorable features like higher sensitivity and selectivity compared to colorimetric detectors, possibility to create ratiometric sensors. At present time many examples of the derivatives of crown and azacrown ethers,[1] calix[4]arene,[2] and thiacalix[4]arene,[3] tetraazamacrocycles[4] bearing fluorescent groups have been described in literature. A special interest paid to 1,4,7-triazacyclononane (TACN) and compounds produced on its basis arises from the application of their metal complexes primarily in the synthesis of bifunctional radiopharmaceuticals capable of selective coordination of ^{111}In, $^{67/68}$Ga, $^{64/67}$Cu, ^{90}Y, and ^{99m}Tc cations[5] which often possess additional chelating carboxylate and phosphonate arms.[6] Till now the data on the fluorescent derivatives of TACN used as chemosensors are quite scarce. One can cite the reports on the tridansyl (dansyl=5-dimethylamino-1-sulphonylnaphthalene) substituted triazacyclononane,[7] benzothiazole derivative bearing two additional pyridylmethyl arms,[8] TACN modified with pyrene fluorophore.[9] The tridansyl derivative was used as a fluorescent chemosensor for Ag(I) and Cu(II) cations, and the compounds bearing this fluorophore group attached to various ionophores were described for the detection of Hg(I),[10] Cu(II),[11] Pb(II),[12] Tl(I), Cs(I),[13] and Hg(I)[14] cations. No information can be found about the synthesis of bicyclic compounds comprising TACN unit and their application for detecting metal ions though cryptand-like structures are of special interest due to their special character of binding cations. In our previous research we successfully applied Pd(0)-catalyzed amination reaction to the synthesis of macrocyclic[15] and polymacrocyclic[16] compounds and began the studies of their coordination abilities towards metal cations. The first examples of the porphyrin-derived conjugates were shown to be promising fluorescent chemosensors for Cu(II) cations.[17] In this work we develop this approach in the synthesis of bicyclic compounds comprising triazacycloalkane units and fluorophore groups.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. UV-Vis spectra were recorded with Agilent Cary 60 spectrophotometer in MeCN, spectra of fluorescence were obtained with Horiba Jobin Yvon Fluoromax 2 spectrofluorometer in acetonitrile (UHPLC grade). 1,4,7-Triazacyclononane (TACN) and 1,5,9-triazacyclododecane (TACD) were provided by CheMatech Co (Dijon, France), 3- and 4-bromobenzyl bromides, trioxadiamine, 1-aza-15-crown-5 ether, *tris*(2-aminoethyl)amine, benzaldehyde, dansyl chloride (dansyl=5-dimethylamino-1-sulphonylnaphthalene), 2-bromo- and 2-(chloromethyl)naphthalene, 9-(bromomethyl)acridine, *rac*-BINAP and DavePhos ligands, sodium *tert*-butoxide, were purchased from Sigma-Aldrich Co and used without further purification, $Pd(dba)_2$ was synthesized according to the method described.[18] Acetonitrile of UHPLC grade was used without additional purification, dioxane was successively distilled over NaOH and sodium. Chloroform was distilled over P_2O_5, dichloromethane was distilled over CaH_2, methanol was used freshly distilled.

*Method for the synthesis of dansyl derivatives of triazacycloalkanes **3**, **4**.* A one-neck flask equipped with a magnetic stirrer was charged with TACN (**1**) or TACD (**2**) (2–3 mmol) in acetonitrile, potassium carbonate and the diluted solution of dansyl chloride in acetonitrile was added slowly dropwise during *ca* 4 h. The residue was filtered off, washed with chloroform (in the case of TACN derivatives) or dichloromethane (in the case of TACD derivatives) (5 ml), the combined organic fractions were evaporated *in vacuo* and chromatographed on silica gel using a sequence of eluents: $CHCl_3$, $CHCl_3$–MeOH 100:1–2:1, $CHCl_3$–MeOH–NH_{3aq} 100:20:1–100:20:2 (for TACN derivative) or CH_2Cl_2, CH_2Cl_2–MeOH 100:1–2:1 (for TACD derivative).

*5-(1,4,7-Triazacyclononan-1-ylsulfonyl)-N,N-dimethylnaphthalene-1-amine (**3**).* Obtained from TACN (**1**) (387 mg, 3 mmol), dansyl chloride (540 mg, 2 mmol) in the presence of potassium carbonate (2070 mg, 15 mmol) in 105 ml acetonitrile. Eluent: $CHCl_3$ – MeOH–NH_{3aq} 100:20:1–100:20:2, yellow viscous oil. Yield 493 mg (68 %). *m/z* (MALDI-TOF) found: 363.1815. $C_{18}H_{27}N_4O_2S$ requires 363.1849 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.94 (2H, br. s, NH), 2.82 (6H, s, CH_3), 2.84 (4H, s, CH_2NH), 3.02–3.06 (4H, m, CH_2NH), 3.33–3.37 (4H, m, CH_2NS), 7.13 (1H, d, ^3J=7.6 Hz, H6(Nf)), 7.45 (1H, dd, ^3J=8.5 Hz, ^3J=7.3 Hz, H3(Nf)), 7.50 (1H, dd, ^3J=8.7 Hz, ^3J=7.6 Hz, H7(Nf)), 7.49 (1H, dd, ^3J=7.3 Hz, ^4J=1.0 Hz, H2(Nf)), 8.43 (1H, d, ^3J=8.7 Hz, H8(Nf)), 8.47 (1H, d, ^3J=8.5 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.2 (2C, CH_3), 49.2 (2C, CH_2NH), 49.3 (2C, CH_2NH), 53.7 (2C, CH_2NS), 115.1 (1C, CH(Nf)), 119.6 (1C, CH(Nf)), 122.9 (1C, CH(Nf)), 127.9 (1C, CH(Nf)), 128.0 (1C, CH(Nf)), 129.9 (1C, CH(Nf)), 130.1 (1C, C(Nf)), 130.2 (1C, C(Nf)), 135.5 (1C, C(Nf)), 151.5 (1C, NC(Nf)).

*5,5'-(1,4,7-Triazacyclononan-1,4-diylsulfonyl)bis(N,N-dimethylnaphthalene-1-amine) (**5**).* Obtained as the second product in the synthesis of compound **3**. Eluent: $CHCl_3$ – MeOH 15:1, yellow viscous oil. Yield 172 mg (29 %). *m/z* (MALDI-TOF) found: 596.2319. $C_{30}H_{38}N_5O_4S_2$ requires 596.2360 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.83 (1H, br. s, NH), 2.85 (12H, s, CH_3), 3.19–3.24 (4H, m, CH_2NH), 3.41–3.45 (4H, m, CH_2NS), 3.67 (4H, s, CH_2NS), 7.16 (2H, d, ^3J=7.6 Hz, H6(Nf)), 7.48 (2H, dd, ^3J=8.5 Hz, ^3J=7.5 Hz, H3(Nf)), 7.53 (2H, dd, ^3J=8.7 Hz, ^3J=7.6 Hz, H7(Nf)), 7.96 (2H, dd, ^3J=7.5 Hz, ^4J=1.0 Hz, H2(Nf)), 8.41 (2H, d, ^3J=8.7 Hz, H8(Nf)), 8.51 (2H, d, ^3J=8.5 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.3 (4C, CH_3), 48.5 (2C, CH_2NH), 52.7 (2C, CH_2NS), 53.7 (2C, CH_2NS), 115.3 (2C, CH(Nf)), 119.4 (2C, CH(Nf)), 120.0 (2C, CH(Nf)), 128.2 (4C, CH(Nf)), 130.2 (4C, C(Nf), CH(Nf)), 130.3 (2C, C(Nf)), 134.2 (2C, C(Nf)), 151.7 (2C, NC(Nf)).

*5-((1,5,9-Triazacyclododecan-1-yl)sulfonyl)-N,N-dimethylnaphthalene-1-amine (**4**).* Obtained from TACD (**2**) (342 mg, 2 mmol) and dansyl chloride (378 mg, 1.4 mmol) in the presence of potassium carbonate (1380 mg, 10 mmol) in 70 ml acetonitrile. Eluent: CH_2Cl_2–MeOH 5:1, yellow viscous oil. Yield 166 mg (28 %). *m/z* (MALDI-TOF) found: 405.2357. $C_{21}H_{33}N_4O_2S$ requires 405.2324 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.83 (2H, quintet, ^3J=5.2 Hz, CCH_2C), 2.06 (4H, quintet, ^3J=5.7 Hz, CCH_2C), 2.84 (6H, s, CH_3), 2.99 (4H, t, ^3J=5.4 Hz, CH_2N), 3.07 (4H, t, ^3J=5.2 Hz, CH_2N), 3.13 (4H, t, ^3J=6.1 Hz, CH_2N), 7.14 (1H, d, ^3J=7.5 Hz, H6(Nf)), 7.47–7.53 (2H, m, H3, H7(Nf)), 8.07 (1H, d, ^3J=7.5 Hz, H2(Nf)), 8.47 (1H, d, ^3J=8.6 Hz, H8(Nf)), 8.55 (1H, d, ^3J=8.5 Hz, H4(Nf)), two NH protons were not unambiguously assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 22.1 (1C, CCH_2C), 25.7 (2C, CCH_2C), 45.1 (2C, CH_2N), 45.3 (2C, CH_3), 49.1 (2C, CH_2N), 50.0 (2C, CH_2N), 115.3 (1C, CH(Nf)), 119.0 (1C, CH(Nf)), 123.0 (1C, CH(Nf)), 128.2 (1C, CH(Nf)), 130.1 (1C, C(Nf)), 130.7 (1C, CH(Nf)), 131.0 (2C, CH(Nf), C(Nf)), 131.2 (1C, C(Nf)), 151.7 (1C, NC(Nf)).

*5,5'-(1,5,9-Triazacyclododecane-1,5-diylsulfonyl)bis(N,N-dimethylnaphthalene-1-amine) (**6**).* Obtained as the second product in the synthesis of compound **4**. Eluent: CH_2Cl_2–MeOH 20:1, yellow crystalline powder, m.p. 158–160 °C. Yield 288 mg (65 %). *m/z* (MALDI-TOF) found: 638.2809. $C_{33}H_{44}N_5O_4S_2$ requires 638.2835 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.67 (4H, quintet, ^3J=5.5 Hz, CCH_2C), 1.87 (4H, quintet, ^3J=6.9 Hz, CCH_2C), 2.61 (2H, t, ^3J=5.4 Hz, CH_2N), 2.87 (12H, s, CH_3), 3.20 (4H, t, ^3J=6.9 Hz, CH_2N), 3.27 (4H, t, ^3J=5.9 Hz, CH_2N), 7.16 (2H, d, ^3J=7.5 Hz, H6(Nf)), 7.47–7.53 (4H, m, H3, H7(Nf)), 8.14 (2H, dd, ^3J=7.3 Hz, ^4J=0.8 Hz, H2(Nf)), 8.35 (2H, d, ^3J=8.7 Hz, H8(Nf)), 8.52 (2H, d, ^3J=8.5 Hz, H4(Nf)), NH proton was not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 23.8 (1C, CCH_2C), 27.8 (2C, CCH_2C), 42.9 (2C, CH_2N), 45.4 (6C, CH_3, CH_2N), 45.8 (2C, CH_2N), 115.1 (2C, CH(Nf)), 119.6 (2C, CH(Nf)), 123.1 (2C, CH(Nf)), 127.9 (2C, CH(Nf)), 130.0 (2C, C(Nf)), 130.1 (2C, CH(Nf)), 130.3 (4C, CH(Nf), C(Nf)), 134.0 (2C, C(Nf)), 135.6 (2C, NC(Nf)).

*Method for the synthesis of dansyl and bromobenzyl derivatives of triazacycloalkanes **7–9**.* A one-neck flask equipped with a magnetic stirrer was charged with a corresponding dansyl derivative of TACN (**3**) or TACD (**4**) which was solubilized in 0.3–0.5 ml dichloromethane, then acetonitrile (2–8 ml) was added to make a solution, followed by potassium carbonate, then appropriate bromobenzyl bromide was added in one portion. The reaction mixture was stirred at ambient temperature for 24 h, then the residue was filtered off, washed with dichloromethane (5 ml), the combined organic fractions were evaporated *in vacuo* and, if necessary, chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2–MeOH 100:1–2:1. In the case when chromatographic purification was unnecessary, the reaction mixture was dissolved in 5 ml dichloromethane, washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness.

*5-(4,7-Bis(3-bromobenzyl)-1,4,7-triazacyclononan-1-ylsulfonyl)-N,N-dimethylnaphthalene-1-amine (**7**).* Obtained from compound **3** (405 mg, 1.12 mmol), 3-bromobenzyl bromide (500 mg, 2 mmol) in the presence of potassium carbonate (770 mg, 5.58 mmol) in 6 ml acetonitrile. Yellow glassy solid. Yield 577 mg (83 %). *m/z* (MALDI-TOF) found: 699.1034. $C_{32}H_{37}Br_2N_4O_2S$ requires 699.1004 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.68 (4H, br. s, CH_2N), 2.84 (6H, s, CH_3), 3.04 (4H, br. s, CH_2N), 3.45 (4H, br. s, CH_2NS), 3.60 (4H, s, $PhCH_2N$), 7.13–7.18 (3H, m, H6(Nf), H5(Ph)), 7.23 (2H, br. s, H6(Ph)), 7.35 (2H, d, ^3J=7.8 Hz, H4(Ph)), 7.44 (2H, br. s, H2(Ph)), 7.47 (1H, dd, ^3J=8.5 Hz, ^3J=7.5 Hz, H3(Nf)), 7.53 (1H, dd, ^3J=8.7 Hz, ^3J=7.7 Hz, H7(Nf)), 8.01 (1H, dd, ^3J=7.5 Hz, ^4J=0.9 Hz, H2(Nf)), 8.43 (1H, d, ^3J=8.7 Hz, H8(Nf)), 8.49 (1H, d, ^3J=8.5 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.1 (2C, CH_3), 50.2 (2C, CH_2N), 54.9 (2C, CH_2N), 55.1 (2C, CH_2N), 61.4 (2C, NCH_2Ph), 115.0 (1C, CH(Nf)), 119.5 (1C, CH(Nf)), 122.1 (2C, C3(Ph)), 122.9 (1C, CH(Nf)), 127.4 (2C, CH(Ph)), 127.8 (1C, CH(Nf)), 128.2 (1C, CH(Nf)), 129.7 (2C, CH(Ph)), 129.8 (1C, CH(Nf)), 130.0 (2CH(Ph), 2C(Nf)), 131.6 (2C, CH(Ph)), 135.0 (1C, C(Nf)), 142.0 (2C, C1(Ph)), 151.4 (1C, C(Nf)).

*5-(4,7-Bis(4-bromobenzyl)-1,4,7-triazacyclononan-1-ylsulfonyl)-N,N-dimethylnaphthalene-1-amine (**8**).* Obtained from compound **3** (340 mg, 0.94 mmol), 4-bromobenzyl bromide (350 mg, 1.5 mmol), in the presence of potassium carbonate (400 mg, 2.90 mmol) in 8 ml acetonitrile. Yellow glassy solid, yield 520 mg (99 %). *m/z* (MALDI-TOF) found: 699.1045. $C_{32}H_{37}Br_2N_4O_2S$ requires 699.1004 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.63 (4H, br. s, CH_2N), 2.84 (6H, s, CH_3) 3.02 (4H, br. s, CH_2N), 3.44 (4H, br. s, CH_2NS), 3.57 (2H, s, $PhCH_2N$), 7.15 (4H, d, ^3J=8.3 Hz, H2, H2'(Ph)), 7.24 (1H, d, ^3J=7.6 Hz, H6(Nf)), 7.39 (4H, d, ^3J=8.3 Hz, H3, H3'(Ph)), 7.46 (1H, dd, ^3J=8.5 Hz, ^3J=7.3 Hz, H3(Nf)), 7.51 (1H, dd, ^3J=8.6 Hz, ^3J=7.6 Hz, H7(Nf)), 7.99 (1H, d, ^3J=7.3 Hz, H2(Nf)), 8.40 (1H, d, ^3J=8.6 Hz, H8(Nf)), 8.49 (1H, d, ^3J=8.5 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.3 (2C, CH_3), 50.2 (2C, CH_2N), 55.2 (2C, CH_2N), 55.4 (2C, CH_2N), 61.7 (2C, $PhCH_2N$), 115.2 (1C, CH(Nf)), 119.6 (1C, CH(Nf)), 120.7 (2C, C4(Ph)), 123.0 (1C, CH(Nf)), 128.0 (1C, CH(Nf)), 128.4 (1C, CH(Nf)), 129.9 (1C, C(Nf)), 130.2 (1C, C(Nf)), 130.7 (4CH(Ph), CH(Nf)), 131.3 (4C, CH(Ph)), 135.1 (1C, C(Nf)), 138.7 (2C, C1(Ph)), 151.6 (1C, NC(Nf)).

*5-((5,9-Bis(3-bromobenzyl)-1,5,9-triazacyclododecan-1-yl)-sulfonyl)-N,N-dimethylnaphthalene-1-amine (**9**).* Obtained from compound **4** (166 mg, 0.41 mmol), 3-bromobenzyl bromide (200 mg, 0.8 mmol), in the presence of potassium carbonate (500 mg, 3.62 mmol) in 4 ml acetonitrile. Eluent: CH_2Cl_2–MeOH 100:1, yellow glassy solid. Yield 113 mg (38 %). *m/z* (MALDI-TOF) found: 741.1449. $C_{35}H_{43}Br_2N_4O_2S$ requires 741.1473 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.57 (4H, br. s, CCH_2C), 1.67 (2H, br. quintet, $^3J_{obs}$=5.1 Hz, CCH_2C), 2.22 (4H, br. t, $^3J_{obs}$=4.9 Hz, CH_2N), 2.58 (4H, br.s, CH_2N), 2.86 (6H, s, CH_3), 3.57 (4H, t, ^3J=7.6 Hz, CH_2N), 3.39 (4H, s, $PhCH_2N$), 7.14–7.18 (5H, m, H6(Nf), H(Ph)), 7.34–7.38 (4H, m, H(Ph)), 7.46 (1H, dd, ^3J=8.5 Hz, ^3J=7.3 Hz, H3(Nf)), 7.51 (1H, dd, ^3J=8.7 Hz, ^3J=7.6 Hz, H7(Nf)), 8.13 (1H, dd, ^3J=7.3 Hz, ^4J=0.9 Hz, H2(Nf)), 8.18 (1H, d, ^3J=8.7 Hz, H7(Nf)), 8.48 (1H, d, ^3J=8.5 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 23.1 (2C, CCH_2C), 23.9 (1C, CCH_2C), 41.3 (2C, CH_2N), 45.4 (2C, CH_3), 48.3 (2C, CH_2N), 51.0 (2C, CH_2N), 57.7 (2C, $PhCH_2N$), 115.0 (1C, CH(Nf)), 119.5 (1C, CH(Nf)), 122.3 (2C, C3(Ph)), 123.1 (1C, CH(Nf)), 127.4 (2C, CH(Ph)), 127.8 (1C, CH(Nf)), 129.5 (1C, CH(Nf)), 129.8 (2C, CH(Ph)), 129.9 (br.s, CH(Nf), 2CH(Ph), 2C(Nf)), 131.8 (2C, CH(Ph)), 135.7 (1C, C(Nf)), 141.8 (2C, C1(Ph)), 151.6 (1C, NC(Nf)).

*Method for the synthesis of the cryptands **11**–**13**.* A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with corresponding triazacycloalkane derivative **7–9**, $Pd(dba)_2$ (16 mol%), DavePhos (18 mol%), absolute dioxane. The mixture was stirred for 2–3 min, then trioxadiamine **10** was added followed by *t*BuONa. The reaction mixture was stirred at reflux for 24 h, cooled down to ambient temperature, the residue was filtered off, washed with dichloromethane (5 ml), combined organic fractions were evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents CH_2Cl_2, CH_2Cl_2–MeOH 100:1–2:1, CH_2Cl_2–MeOH– NH_{3aq}100:20:1–10:4:1.

*5-(10,13,16-Trioxa-6,20-diaza-3(1,4)-triazacyclononane-1,5(1,3)-dibenzenocycloicosaphan-3^7-ylsulfonyl)-N,N-dimethylnaphthalenyl-1-amine (**11**).* Obtained from compound **7** (140 mg, 0.2 mmol), trioxadiamine **10** (44 mg, 0.2 mmol), in the presence of $Pd(dba)_2$ (18 mg, 0.032 mmol), DavePhos (14 mg, 0.036 mmol), *t*BuONa (58 mg, 0.6 mmol) in 10 ml dioxane. Eluent: CH_2Cl_2–MeOH 3:1, yield 37 mg (24 %), yellow glassy solid. UV-Vis (CH_3CN) λ_{max} (logε) nm: 305 (3.76), 340 (3.48). *m/z* (MALDI-TOF) found: 759.4223. $C_{42}H_{59}N_6O_5S$ requires 759.4268 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.85 (4H, br. quintet, $^3J_{obs}$=5.7 Hz, $CH_2CH_2CH_2$), 2.86 (4H, br. s, CH_2N), 2.87 (6H, s, CH_3) 3.08–4.00 (12H, br. m, CH_2N, $PhCH_2N$), 3.24 (4H, br. t, $^3J_{obs}$=4.8 Hz, CH_2NPh), 3.55–3.60 (8H, br. m, CH_2O), 3.61–3.66 (4H, br. m, CH_2O), 6.58 (2H, br. s, H(Ph)), 6.60 (2H, br. d, $^3J_{obs}$=6.9 Hz, H(Ph)), 6.84 (2H, br. s, H2(Ph)), 7.10 (2H, t, ^3J=7.7 Hz, H5(Ph)), 7.15 (1H, d, ^3J=7.6 Hz, H6(Nf)), 7.49 (1H, t, $^3J_{obs}$=7.8 Hz, H3(Nf)), 7.53 (1H, t, $^3J_{obs}$=8.2 Hz, H7(Nf)), 7.98 (1H, br. s, H2(Nf)), 8.34 (1H, br. d, ^3J=7.6 Hz, H8(Nf)), 8.54 (1H, br. d, ^3J=8.2 Hz, H4(Nf)), two NH protons were not unambiguously assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.7 (2C, CCH_2C), 41.4 (2C, CH_2NPh), 45.3 (2C, CH_3), 47.0–57.0 (6C, br. m, CH_2N), 61.7 (2C, br. s, $\Delta\nu_{1/2}$=100 Hz, $PhCH_2N$), 69.4 (2C, CH_2O), 70.1 (2C, CH_2O), 70.5 (2C, CH_2O), 112.7 (2C, br. s, $\Delta\nu_{1/2}$=60 Hz, CH(Ph)), 114.3 (2C, br. s, $\Delta\nu_{1/2}$=30 Hz, (CH(Ph)), 115.4 (1C, CH(Nf)), 118.1 (2C, CH(Ph)), 119.0 (1C, br. s, $\Delta\nu_{1/2}$=30 Hz, CH(Nf)), 123.1 (1C, (CH(Nf)), 128.2–131.0 (br. m, 3CH(Nf), 2C5(Ph), 2C(Nf)), 134.4 (1C, C(Nf)), 137.5 (2C, C1(Ph)), 149.2 (2C, br. s, $\Delta\nu_{1/2}$=20 Hz, C3(Ph)), 151.9 (1C, NC(Nf)).

*5-(10,13,16-Trioxa-6,20-diaza-3(1,4)-triazacyclononan-1,5(1,4)-dibenzenocycloicosaphan-3⁷-ylsulfonyl)-N,N-dimethylnaphthalene-1-amine (**12**).* Obtained from compound **8** (125 mg, 0.178 mmol), trioxadiamine **10** (39 mg, 0.178 mmol), in the presence of $Pd(dba)_2$ (16 mg, 0.028 mmol), DavePhos (13 mg, 0.032 mmol), *t*BuONa (51 mg, 0.53 mmol), in 10 ml dioxane. Eluent: CH_2Cl_2–MeOH 2:1, yield 21 mg (15 %), yellow glassy solid. UV-Vis (CH_3CN) λ_{max} (lgε) nm: 305 (3.56), 340 (3.48). *m/z* (MALDI-TOF) found: 759.4223. $C_{42}H_{59}N_6O_5S$ requires 759.4268 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.88 (4H, br. quintet, $^3J_{obs}$=5.7 Hz, CCH_2C), 2.88 (6H, s, CH_3), 3.10–4.00 (16H, br. m, CH_2N, $PhCH_2N$), 3.26 (4H, br. t, $^3J_{obs}$=5.8 Hz, CH_2NPh), 3.58–3.63 (8H, m, CH_2O), 3.67–3.71 (4H, m, CH_2O), 4.52 (2H, br. s, NH), 6.55 (4H, d, $^3J_{obs}$=8.1 Hz, H2, H2'(Ph)), 7.03 (4H, br. s, H3, H3'(Ph)), 7.19 (1H, d, $^3J_{obs}$=7.3 Hz, H6(Nf)), 7.52 (1H, t, $^3J_{obs}$=8.0 Hz, H3(Nf)), 7.55 (1H, t, $^3J_{obs}$=7.9 Hz, H7(Nf)), 8.04 (1H, br. s, H2(Nf)), 8.31 (1H, d, $^3J_{obs}$=8.8 Hz, H8(Nf)), 8.56 (1H, d, $^3J_{obs}$=8.6 Hz, H4(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.7 (2C, CCH_2C), 42.1 (CH_2NHPh), 45.4 (2C, CH_3), 47.9–53.5 (6C, br. m, CH_2N), 60.6 (2C, br. s, $\Delta\nu_{1/2}$= 50 Hz, $PhCH_2N$), 70.1 (2C, CH_2O), 70.2 (2C, CH_2O), 70.7 (2C, CH_2O), 112.9 (4C, CH(Ph)), 115.5 (1C, CH(Nf)), 118.7 (1C, CH(Nf)), 123.1 (1C, CH(Nf)), 128.6 (1C, CH(Nf)), 130.1 (1C, C(Nf)), 130.3 (2C, C1(Ph)), 130.7 (1C, C(Nf)), 131.1 (1C, C(Nf)), 131.6 (6C, 4CH(Ph), 2CH(Nf)), 149.0 (2C, C4(Ph)), 152.0 (1C, NC(Nf)).

*5-(10,13,16-Trioxa-3¹,3⁵,3⁹,6,20-pentaaza-3(1,5)-cyclododecana-1,5(1,3)-dibenzenocycloicosaphan-3⁹-ylsulfonyl)-N,N-dimethylnaphthalene-1-amine (**13**).* Obtained from compound **9** (113 mg, 0.152 mmol), trioxadiamine **10** (33 mg, 0.152 mmol), in the presence of $Pd(dba)_2$ (14 mg, 0.0243 mmol), DavePhos (11 mg, 0.0274 mmol), *t*BuONa (58 mg, 0.608 mmol), in 10 ml dioxane. Eluent: CH_2Cl_2–MeOH 10:1, yield 32 mg (26 %), yellow glassy solid. UV-Vis (CH_3CN) λ_{max} (logε) nm: 305 (3.59), 340 (3.43). *m/z* (MALDI-TOF) found: 801.4761. $C_{45}H_{65}N_6O_5S$ requires 801.4737 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.50–2.70 (14H, br. m, $NCCH_2CN$, CH_2N), 1.87 (4H, quintet, ^3J=6.3 Hz, $NCCH_2CO$), 2.88 (6H, s, CH_3), 3.10–3.70 (20H, br. m, CH_2O, CH_2N, $PhCH_2N$), 3.20 (4H, t, ^3J=5.6 Hz, CH_2NPh), 6.44 (2H, d, ^3J=7.2 Hz, H(Ph)), 6.49 (2H, d, ^3J=8.2 Hz, H(Ph)), 6.85 (2H, br. s, H2(Ph)), 7.05 (2H, t, ^3J=7.8 Hz, H5(Ph)), 7.19 (1H, d, ^3J=7.6 Hz, H6(Nf)), 7.49–7.60 (2H, m, H3, H7(Nf)), 8.07 (1H, d, ^3J=7.3 Hz, H2(Nf)), 8.41 (1H, br. d, $^3J_{obs}$=8.3 Hz, H8(Nf)), 8.55 (1H, d, ^3J=8.2 Hz, H4(Nf)), two NH protons were not unambiguously assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.2 (3C, br. s, $\Delta\nu_{1/2}$= 30 Hz, $NCCH_2CN$), 29.1 (2C, $NCCH_2CO$), 41.4 (2C, CH_2NPh), 45.3 (2C, CH_3), 46.9 (2C, br. s, $\Delta\nu_{1/2}$= 30 Hz, CH_2N), 47.7 (2C, br. s, $\Delta\nu_{1/2}$= 30 Hz, CH_2N), 48.5 (2C, br. s, $\Delta\nu_{1/2}$= 30 Hz, CH_2N), 58.7 (2C, $PhCH_2N$), 69.6 (2C, CH_2O), 70.2 (2C, CH_2O), 70.6 (2C, CH_2O), 112.1 (2C, CH(Ph)), 113.6 (2C, CH(Ph)), 115.3 (1C, CH(Nf)), 117.7 (2C, CH(Ph)), 119.3 (1C, CH(Nf)), 123.2 (1C, CH(Nf)), 128.3 (1C, CH(Nf)), 129.4 (2C, CH(Ph)), 129.6 (1C, CH(Nf)), 130.1 (1C, C(Nf)), 130.3 (1C, C(Nf)), 130.7 (1C, CH(Nf)), 133.6 (1C, br. s, C(Nf)), 149.3 (2C, C3(Ph)), 151.9 (1C, NC(Nf)), quaternary carbon atom C1(Ph) was not unambiguously assigned.

*10-Phenyl-1,4,7-triazabicyclo[5.2.1]decane (**14**).*[19] A one-neck flask equipped with a magnetic stirrer was charged with 1,4,7-triazacyclononane (645 mg, 5 mmol), 120 ml of ethanol, freshly distilled benzaldehyde (0.5 ml, 4.9 mmol) was added followed by molecular sieves, the mixture was stirred for 6 h. The residue was filtered off, washed with ethanol (10 ml), combined organic fractions were evaporated *in vacuo* to give compound **14** as pale-yellow crystals, m.p. 103–104 °C. Yield 910 mg (86 %).

*4-(Naphthalen-2-ylmethyl)-10-phenyl-1,4,7-triazabicyclo[5.2.1]decane (**15**).* A one-neck flask equipped with a magnetic stirrer was charged with compound **14** (217 mg, 1 mmol), dissolved in MeCN (20 ml), 2-(bromomethyl) naphthalene (221 mg, 1 mmol) was added followed by K_2CO_3 (345 mg, 2.5 mmol), the reaction was stirred for 24 h, the residue was filtered off, washed with CH_2Cl_2 (10 ml), combined organic fractions were evaporated *in vacuo* to give compound **15** as a yellow oil. Yield 339 mg (95 %). *m/z* (MALDI-TOF) found: 358.2256. $C_{24}H_{28}N_3$ requires 358.2283 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.74 (2H, dt, ^2J=14.9 Hz, ^3J=2.7 Hz, CH_2N), 2.94 (2H, dt, ^2J=14.9 Hz, ^3J=2.2 Hz, CH_2N), 2.99–3.08 (4H, m, CH_2N), 3.14–3.20 (2H, m, CH_2N), 3.33–3.42 (2H, m, CH_2N), 3.97 (2H, s, CH_2Nf), 5.77 (1H, s, CHPh), 7.31 (1H, t, ^3J=7.4 Hz, H4(Ph)), 7.34 (2H, t, $^3J_{obs}$=7.6 Hz, H3, H3'(Ph)), 7.45–7.49 (2H, m, H(Nf)), 7.51 (1H, d, ^3J=8.1 Hz, H(Nf)), 7.55–7.58 (2H, m, H2, H2'(Ph)), 7.72 (1H, s, H1(Nf)), 7.80–7.85 (3H, m, H(Nf). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 49.2 (2C, CH_2N), 54.9 (2C, CH_2N), 56.3 (2C, CH_2N), 62.5 (1C, CH_2Nf), 87.5 (1C, CHPh), 125.5 (1C, CH(Nf)), 125.9 (1C, CH(Nf)), 126.4 (3C, CH(Ph), C3, C3'(Ph)), 126.8 (1C, CH(Nf)), 126.9 (1C, CH(Nf)), 127.6 (2C, CH(Nf)), 127.9 (2C, C2, C2'(Ph)), 128.0 (1C, CH(Nf)), 132.7 (1C, C(Nf)), 133.2 (1C, C(Nf)), 137.8 (1C, C2(Nf)), 145.4 (1C, C1(Ph)).

*1-(Naphthalenylmethyl)-1,4,7-triazacyclononane trihydrochloride (**16**).* Synthesized from compound **15** (357 mg, 1 mmol) by stirring with 15 ml 1M HCl for 4 h. The solution was evaporated *in vacuo*, the crystalline residue was washed with 10 ml chloroform and dried *in vacuo*. White crystalline powder, yield 377 mg (94 %). ^1H NMR (D_2O, 298 K) δ_H ppm: 2.94–2.98 (4H, m, CH_2N), 3.11–3.15 (4H, m, CH_2N), 3.57 (4H, s, CH_2N), 3.95 (2H, s, CH_2Nf), 7.48–7.55 (3H, m, H(Nf)), 7.80 (1H, br.s, H1(Nf)), 7.85–7.90 (3H, s, H(Nf)). ^{13}C NMR (D_2O, 298 K) δ_c ppm: 42.2 (2C, CH_2N), 43.6 (2C, CH_2N), 47.7 (2C, CH_2N), 59.2 (1C, CH_2Nf), 126.6 (1C, CH(Nf)), 126.7 (1C, CH(Nf)), 127.7 (1C, CH(Nf)), 127.9 (2C, CH(Nf)), 128.4 (1C, CH(Nf)), 129.2 (1C, CH(Nf)), 132.6 (1C, C(Nf)), 132.8 (1C, C(Nf)), 132.9 (1C, C(Nf)).

*1-(Naphthalen-2-ylmethyl)-1,4,7-triazacyclononane (**17**).* Synthesized from compound **16** (377 mg, 0.94 mmol) by stirring with NaOH (109 mg, 2.72 mmol) in 5 ml water for 2 min followed by extraction with chloroform (4×50 ml), combined organic fractions were evaporated *in vacuo* to obtain yellow-brown glassy compound. Yield 216 mg (86 %). *m/z* (MALDI-TOF) found: 270.1935. $C_{17}H_{24}N_3$ requires 270.1970 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.68 (8H, br.s, CH_2N), 2.82 (4H, br.s, CH_2N), 3.85 (2H, s, CH_2Nf), 7.41–7.45 (2H, m, H(Nf)), 7.50 (1H, d, ^3J=8.5 Hz, H(Nf)), 7.68 (1H, br.s, H1(Nf)), 7.77–7.82 (3H, m, H(Nf)), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.9 (2C, CH_2N), 46.1 (2C, CH_2N), 52.2 (2C, CH_2N), 61.7 (1C, CH_2Nf), 125.6 (1C, CH(Nf)), 126.0 (1C, CH(Nf)), 127.2 (1C, CH(Nf)), 127.4 (1C, CH(Nf)), 127.6 (2C, CH(Nf)), 128.1 (1C, CH(Nf)), 132.7 (1C, C(Nf)), 133.2 (1C, C(Nf)), 136.8 (1C, C2(Nf)).

*1,4-Bis(3-bromobenzyl)-7-(naphthalene-2-ylmethyl)-1,4,7-triazacyclononane (**18**).* A one-neck flask equipped with a magnetic stirrer was charged with compound **17** (200 mg, 0.743 mmol), dissolved in MeCN (4 ml), 3-bromobenzyl bromide (280 mg, 1.1 mmol) was added followed by K_2CO_3 (345 mg, 2.5 mmol), the reaction was stirred for 24 h, the residue was filtered off, washed with CH_2Cl_2 (5 ml), combined organic fractions were evaporated *in vacuo* to give compound **18** as a yellow oil. Yield 301 mg (90 %). *m/z* (MALDI-TOF) found: 606.1128. $C_{31}H_{34}Br_2N_3$ requires 606.1119 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.78 (4H, br.s, CH_2N), 2.81 (4H, br.s, CH_2N), 2.86 (4H, br.s, CH_2N), 3.57 (4H, s, NCH_2Ph), 3.80 (2H, br.s, CH_2Nf), 7.15 (2H, t, $^3J_{obs}$=7.8 Hz, H5(Ph)), 7.23 (2H, d, ^3J=7.7 Hz, H6(Ph)), 7.37 (2H, d, ^3J=7.8 Hz, H4(Ph)), 7.42–7.47 (2H, m, H(Nf)), 7.49 (2H, br.s, H2(Ph)), 7.55 (1H, d, ^3J=8.5 Hz, H(Nf)), 7.69 (1H, br.s, H1(Nf)), 7.78–7.84 (3H, m, H(Nf)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 55.2 (6C, br, CH_2N), 62.2 (2C, $PhCH_2N$), 63.0 (1C, CH_2Nf), 122.3 (2C, C3(Ph)), 125.6 (1C, CH(Nf)), 125.9 (1C, CH(Nf)), 127.6 (6C, br, CH(Ph), 4CH(Nf)), 127.8 (1C, CH(Nf)), 129.7 (2C, CH(Ph)), 129.9 (2C, CH(Ph)), 131.9 (2C, CH(Ph)), 132.7 (2C, C(Nf)), 133.2 (1C, C(Nf)), 142.6 (2C, C1(Ph)).

3⁷-(Naphthalen-2-ylmethyl)-10,13,16-trioxa-6,20-diaza-3(1,4)-triazacyclononane-1,5(1,3)-dibenzenacycloicosaphane ***(19)***. Obtained according to a general procedure for macrocyclization from compound **18** (121 mg, 0.2 mmol), trioxadiamine **10** (44 mg, 0.2 mmol) in the presence of $Pd(dba)_2$ (18 mg, 0.032 mmol), DavePhos (14 mg, 0.036 mmol), *t*BuONa (77 mg, 0.8 mmol) in 10 ml of dioxane. Eluent: CH_2Cl_2 – MeOH 5:1, yield 7 mg (6 %), yellow glassy solid. *m/z* (MALDI-TOF) found: 666.4360. $C_{41}H_{56}N_5O_3$ requires 666.4383 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.83 (4H, quintet, ^3J=5.7 Hz, CCH_2C), 2.85 (4H, br.s, CH_2N), 3.08 (4H, br.s, CH_2N), 3.27 (4H, t, ^3J=5.9 Hz, CH_2NPh), 3.45–3.75 (18H, m, CH_2O, CH_2N), 3.82 (2H, br.s, $NfCH_2N$), 6.35–6.82 (4H, m, H(Ph)), 6.62 (2H, d, ^3J=8.2 Hz, H(Ph)), 7.15 (2H, t, ^3J=7.8 Hz, H5(Ph)), 7.45–7.52 (3H, m, H(Nf)), 7.66 (1H, s, H1(Nf)), 7.79–7.83 (3H, m, H(Nf)), two NH protons were not assigned.

9-((1,4,7-Triazacyclononan-1-yl)methyl)acridine ***(21)***. A one-neck flask equipped with a magnetic stirrer was charged with compound **14** (54 mg, 0.25 mmol), dissolved in MeCN (6 ml), 9-(bromomethyl)acridine (68 mg, 0.25 mmol) was added followed by K_2CO_3 (86 mg, 0.625 mmol), the reaction was stirred for 24 h, the residue was filtered off, washed with CH_2Cl_2 (5 ml), combined organic fractions were evaporated *in vacuo* and the residue was chromatographed on silica gel. Eluent: CH_2Cl_2–MeOH–NH_{3aq} 100:20:2, yield 42 mg (52 %), yellow glassy solid. *m/z* (MALDI-TOF) found: 321.2135. $C_{20}H_{25}N_4$ requires 321.2079 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.54 (4H, t, ^3J=5.5 Hz, CH_2N), 2.72 (4H, s, CH_2N), 2.75 (4H, t, ^3J=5.5 Hz, CH_2N), 4.34 (2H, br.s, NH), 4.64 (2H, s, $AcrCH_2N$), 7.56–7.60 (2H, m, H(Acr)), 7.70–7.73 (2H, m, H(Acr)), 8.18 (2H, d, ^3J=8.7 Hz, H1, H8(Acr)), 8.39 (2H, d, ^3J=8.8 Hz, H4, H5(Acr)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 44.3 (2C, CH_2N), 45.3 (2C, CH_2N), 51.8 (2C, CH_2N), 52.1 (1C, $NfCH_2N$), 124.2 (2C, CH(Acr)), 125.7 (2C, C(Ar)), 126.4 (2C, CH(Acr)), 129.8 (2C, CH(Acr)), 130.3 (2C, CH(Acr)), 140.4 (1C, C9(Acr)), 148.5 (2C, C(Acr)).

1,4,7-Tris(acridin-9-ylmethyl)-1,4,7-triazacyclononane ***(23)***. Obtained as the second product in the synthesis of compound **21**. Eluent: CH_2Cl_2–MeOH 10:1, yield 20 mg (34 %), yellow glassy solid. *m/z* (MALDI-TOF) found: 703.3588. $C_{48}H_{43}N_6$ requires 703.3549 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.65 (12H, s, CH_2N), 4.25 (6H, s, $AcrCH_2N$), 7.44–7.47 (2H, m, H(Acr)), 7.71–7.75 (2H, m, H(Acr)), 8.20 (2H, d, ^3J=8.7 Hz, H1, H8(Acr)), 8.30 (2H, d, ^3J=8.8 Hz, H4, H5(Acr)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 53.5 (3C, $AcrCH_2N$), 55.4 (6C, CH_2N), 125.1 (2C, CH(Acr)), 125.6 (2C, CH(Acr)), 125.9 (2C, C(Acr)), 129.7 (2C, CH(Acr)), 130.1 (2C, CH(Acr)), 142.0 (1C, C9(Acr)), 148.6 (2C, C(Acr)).

9-((4,7-Bis(3-bromobenzyl)-1,4,7-triazacyclononan-1-yl) methyl)acridine ***(24)***. A one-neck flask equipped with a magnetic stirrer was charged with compound **21** (53 mg, 0.166 mmol), dissolved in MeCN (3 ml), 3-bromobenzyl bromide (50 mg, 0.2 mmol) was added followed by K_2CO_3 (138 mg, 1 mmol), the reaction was stirred for 24 h, the residue was filtered off, washed with CH_2Cl_2 (5 ml), combined organic fractions were evaporated *in vacuo* to give compound **24** as a yellow oil. Yield 79 mg (72 %). *m/z* (MALDI-TOF) found: 657.1176. $C_{34}H_{35}Br_2N_4$ requires 657.1228 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.63 (4H, s, CH_2N), 2.63–2.68 (4H, m, CH_2N), 2.83–2.88 (4H, m, CH_2N), 3.38 (4H, s, $PhCH_2N$), 4.50 (2H, s, $AcrCH_2N$), 7.10 (4H, d, $^3J_{obs}$=5.2 Hz, H4, H6(Ph)), 7.30–7.34 (2H, m, H5(Ph)), 7.37 (2H, br.s, H2(Ph)), 7.52–7.56 (2H, m, H(Acr)), 7.73–7.76 (2H, m, H(Acr)), 8.22 (2H, d, ^3J=8.3 Hz, H1, H8(Acr)), 8.47 (2H, d, ^3J=8.8 Hz, H4, H5(Acr)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 53.6 (1C, $AcrCH_2N$), 54.8 (4C, CH_2N), 55.8 (2C, CH_2N), 62.0 (2C, $PhCH_2N$), 122.2 (2C, (C3(Ph)), 125.1 (2C, CH(Acr)), 125.7 (2C, CH(Acr)), 125.9 (2C, C(Acr)), 127.4 (2C, CH(Ph)), 129.7 (4C, CH(Ph)), 129.9 (2C, CH(Acr)), 130.1 (2C, CH(Acr)), 137. 2 (2C, CH(Ph)), 142.0 (1C, C9(Acr)), 142.4 (2C, C1(Ph)), 148.6 (2C, C(Acr)).

3⁷-(Acridin-9-ylmethyl)-10,13,16-trioxa-6,20-diaza-3(1,4)-triazacyclononane-1,5(1,3)-dibenzenacycloicosaphane ***(25)***. Obtained according to a general procedure for macrocyclization from compound **24** (79 mg, 0.12 mmol), trioxadiamine **10** (27 mg, 0.12 mmol) in the presence of $Pd(dba)_2$ (11 mg, 0.0192 mmol), DavePhos (9 mg, 0.0216 mmol), *t*BuONa (46 mg, 0.48 mmol) in 8 ml dioxane. Eluent: CH_2Cl_2–MeOH 5:1, yield 8 mg (9 %), yellow glassy solid. *m/z* (MALDI-TOF) found: 717.4547. $C_{44}H_{57}N_6O_3$ requires 717.4492 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.82 (4H, quintet, ^3J=5.8 Hz, CCH_2C), 2.60–3.90 (28H, m, CH_2N, CH_2O), 3.21 (4H, t, ^3J= 5.9 Hz, CH_2NNPh), 4.72 s (2H, s, $AcrCH_2N$), 6.30–6.75 (6H, m, H(Ph)), 7.11 (2H, br.s, H5(Ph)), 7.65–7.70 (2H, m, H(Acr)), 7.78–7.83 (2H, m, H(Acr)), 8.26 (2H, d, ^3J=8.3 Hz, H1, H8(Acr)), 8.49 (2H, d, ^3J=8.1 Hz, H4, H5(Acr)), two NH protons were not assigned.

1,4,7-Tris(3-bromobenzyl)-1,4,7-triazacyclononane ***(26)***. A one-neck flask equipped with a magnetic stirrer was charged with TACN (129 mg, 1 mmol), dissolved in MeCN (8 ml), 3-bromobenzyl bromide (750 mg, 3 mmol) was added followed by K_2CO_3 (690 mg, 5 mmol), the reaction was stirred for 24 h, the residue was filtered off, washed with CH_2Cl_2 (10 ml), combined organic fractions were evaporated *in vacuo* to give compound **26** as a colourless oil. Yield 623 mg (98 %). *m/z* (MALDI-TOF) found: 634.0124. $C_{27}H_{31}Br_3N_3$ requires 634.0068 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.77 (12H, s, CH_2N), 3.56 (6H, s, $PhCH_2N$), 7.16 (3H, t, ^3J=7.7 Hz, H5(Ph)), 7.24 (3H, d, ^3J=7.6 Hz, H6(Ph)), 7.35 (3H, d, ^3J=7.8 Hz, H4(Ph)), 7.48 (3H, br.s, H2(Ph)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 55.3 (6C, CH_2N), 62.3 (3C, $PhCH_2N$), 122.3 (3C, C3(Ph)), 127.5 (3C, CH(Ph)), 129.7 (3C, CH(Ph)), 129.9 (3C, CH(Ph)), 131.8 (3C, CH(Ph)), 142.7 (3C, C1(Ph)).

1,4,7-Tris(3-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)benzyl)-1,4,7-triazacyclononane ***(28)***. A two-necked flask flushed with argon was charged with compound **26** (127 mg, 0.2 mmol), 1-aza-15-crown-5 ether (**27**) (131 mg, 0.6 mmol), $Pd(dba)_2$ (28 mg, 0.048 mmol), DavePhos (21 mg, 0.054 mmol), dioxane (1 ml) was added followed by *t*BuONa (86 mg, 0.9 mmol). The reaction mixture was stirred at reflux for 24 h, then cooled down to ambient temperature, diluted with 5 ml dichloromethane, the residue was filtered off, washed with 5 ml dichloromethane, the combined organic fractions were evaporated *in vacuo* and the residue was chromatographed on silica gel. Eluent: CH_2Cl_2–MeOH–NH_{3aq} 100:20:3, yield 25 mg (12 %), pale-yellow glassy solid. *m/z* (MALDI-TOF) found: 1051.6774. $C_{57}H_{91}N_6O_{12}$ requires 1051.6695 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.87 (12H, br.s, CH_2N), 3.57 (12H, t, ^3J=6.1 Hz, CH_2NPh), 3.58–3.67 (42H, m, CH_2O, $PhCH_2N$), 3.72 (12H, t, ^3J=6.1 Hz, CH_2O), 6.55 (6H, br.d, $^3J_{obs}$=7.2 Hz, H4, H6(Ph)), 6.69 (3H, br.s, H2(Ph)), 7.12 (3H, t, ^3J=7.8 Hz, H5(Ph)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 52.5 (6C, CH_2NPh), 54.5 (6C, br, $\Delta\upsilon_{1/2}$=200 Hz, CH_2N), 62.8 (3C, br, $\Delta\upsilon_{1/2}$=60 Hz, $PhCH_2N$), 68.6 (6C, CH_2O), 70.0 (6C, CH_2O), 70.1 (6C, CH_2O), 71.2 (6C, CH_2O), 110.5 (3C, CH(Ph)), 112.3 (3C, CH(Ph)), 116.6 (3C, CH(Ph)), 129.2 (3C, C5(Ph)), 147.8 (3C, C3(Ph)). Quaternary carbon atoms C1(Ph) were not assigned.

1,4,11,14,17,24,33-Heptaazahexacyclo[12.12.9.2⁴,²⁴.1⁶,¹⁰.1¹⁸,²².1²⁸,³²]tetraconta-6(40),7,9,18(39),19,21,28(36),29,31-nonane ***(30)***. Obtained according to a general procedure for macrocyclization from compound **26** (127 mg, 0.2 mmol), *tris*(2-aminoethyl)amine (**29**) (27 mg, 0.12 mmol) in the presence of $Pd(dba)_2$ (28 mg, 0.048 mmol), DavePhos (21 mg, 0.054 mmol), *t*BuONa (86 mg, 0.9 mmol) in 10 ml of dioxane. Eluent: CH_2Cl_2–MeOH 2:1, yield 15 mg (14 %), yellow oil. *m/z* (MALDI-TOF) found: 540.3854. $C_{33}H_{46}N_7$. requires 540.3815 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.95 (12H, br.s, CH_2N), 3.16 (12H, br.s, CH_2N), 3.54 (6H, s, $PhCH_2N$), 4.97 (3H, br.s, NH), 6.07 (3H, br.s, H2(Ph)), 6.54 (3H, d, ^3J=7.7 Hz, H(Ph)), 6.59 (3H, d, ^3J=7.3 Hz, H(Ph)), 7.18 (3H, t, ^3J=7.7 Hz, H5(Ph)). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 40.9 (3C, CH_2NPh), 48.5 (6C, CH_2N), 50.0 (3C, CH_2N), 60.6 (3C, $PhCH_2N$), 110.2 (3C, CH(Ph)), 116.1 (3C, CH(Ph)), 120.6 (3C, CH(Ph)), 129.9 (3C, C5(Ph)), 135.2 (3C, C1(Ph)), 148.1 (3C, C3(Ph)).

The investigations of the spectral properties of the bicycles **11–13** in the presence of 20 metal salts were carried out in a following manner: 3 ml of the solution of the corresponding bicycle (*C*=21.9 μM for **11**, 21.1 μM for **12**, 15.9 μM for **13**) in MeCN were placed in a spectrofluorimetric cuvette, solutions of appropriate metal salts (Li(I), Na(I), K(I), Mg(II), Ca(II), Ba(II), Al(III), Fe(II), Mn(II), Co(II), Ni(II), Cr(III), Cu(II), Zn(II), Cd(II), Pb(II), Hg(II) perchlorates and Ga(III), In(III), Y(III) nitrates) in MeCN (*C*=0.01 M) were added sequentially (1, 2, 5, 10 equiv.) and after each addition UV-Vis and fluorescence spectra were recorded.

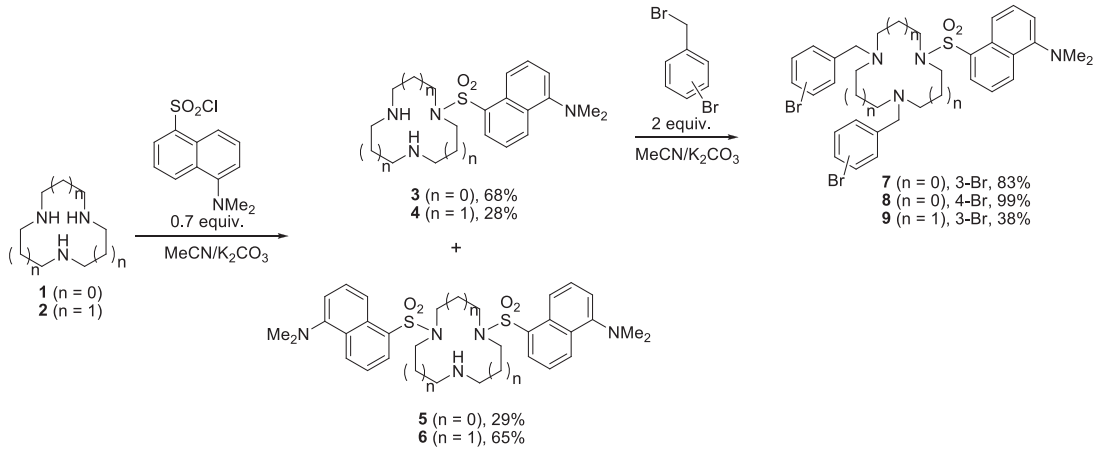
Results and Discussion

For the synthesis of bicyclic derivatives of triazacycloalkanes we intended to modify them with one fluorophore group at the first step and with two bromobenzyl groups at the second step for the accomplishment of the catalytic macrocyclization at the final step. Our investigation started from the synthesis of *N*-dansyl substituted TACN and TACD. For this purpose starting free triazacycloalkanes **1** and **2** were reacted with dansyl chloride in MeCN at room temperature in the presence of K_2CO_3 (Scheme 1). To ensure a sufficient yield of the monodansylated products **3** and **4** the following precautions are to be taken into consideration: 1) the application of no more than 0.7–0.75 equiv. of dansyl chloride is important to diminish the formation of di- and tridansyl substituted by-products; 2) enough diluted solution of dansyl chloride (*C*=0.01 M) should be added very slowly during several hours to a solution of compounds **1** or **2** to prevent an easy formation of indicated by-products; 3) only extra-pure MeCN should be used to exclude the traces of acrylonitrile which readily reacts with TACN and TACD under reaction conditions diminishing the yields of the target products; 4) only chloroform can be used for chromatographic isolation of compound **3** as it readily reacts with dichloromethane forming bicyclic aminal.

In the case of TACN the yield of compound **3** was 68 % while the *N,N'*-didansyl derivative **5** was isolated in 29 % yield. However, TACD was prone for polysubstitution even in the presence of 0.7 equiv. of dansyl chloride, thus the yield of the target product was only 28 % and the second product **6** was obtained in 65 % yield. All compounds were isolated by column chromatography on silica gel. Further reactions of compound **3** with 3- and 4-bromobenzyl bromides proceeded smoothly affording corresponding *bis*(bromobenzyl) substituted TACN **7** and **8** in high yields, but the reaction of TACD derivative **4** with 3-bromobenzyl bromide was complicated with the formation of mono- and tribenzylated by-products what led to a necessity of chromatographic separation and gave the desired compound in 38 % yield.

Catalytic macrocyclization reactions of compound **7** was first carried out with linear trioxadiamine **10** using a standard protocol in the presence of a traditional $Pd(dba)_2$/BINAP (dba=dibenzylideneacetone, BINAP=2,2'-*bis*(diphenylphosphino)-1,1'-binaphthalene) system (Scheme 2). The yield of the macrocycle **11** was 30 % in the reaction mixture and after column chromatography it was isolated in 16 % yield. The change of BINAP for a more electron-rich phosphine ligand, *i.e.* DavePhos (2-(dicyclohexylphosphino)-2'-dimethylaminobiphenyl) did not notably increased the yield in the reaction mixture (32 %) but helped to improve the result after chromatographic isolation (24 %) probably due to a change in the composition of by-products which affect the efficacy of chromatography. The reaction of the same trioxadiamine with *bis*(4-bromobenzyl) derivative **8** catalyzed by $Pd(dba)_2$/DavePhos system provided 27 % yield of compound **12** in the reaction mixture and 15 % yield after its separation. Supposedly, the macrocyclization processes involving di(3-bromobenzyl) substituted precursors are generally more successful than those with isomeric di(4-bromobenzyl) derivatives, probably due to a longer intramolecular distance between two reaction centers in the latter case. This fact was earlier observed in our works.[20] Macrocyclization with TACD derivative **9** was the most successful as it provided 26 % yield of the macrobicycle **13** after isolation.

^{1}H NMR spectra of compounds **11, 12** registered in $CDCl_3$ at 298 K possess a very broad multiplet in 3.0–4.0 ppm region which is associated with CH_2 protons in triazacyclononane ring and in benzyl groups. Signals of some other aromatic protons in benzyl spacers are also notably broadened contrary to aromatic protons in dansyl fluorophore. Analogously, in ^{13}C NMR spectra the signals of corresponding carbon atoms are also more or less

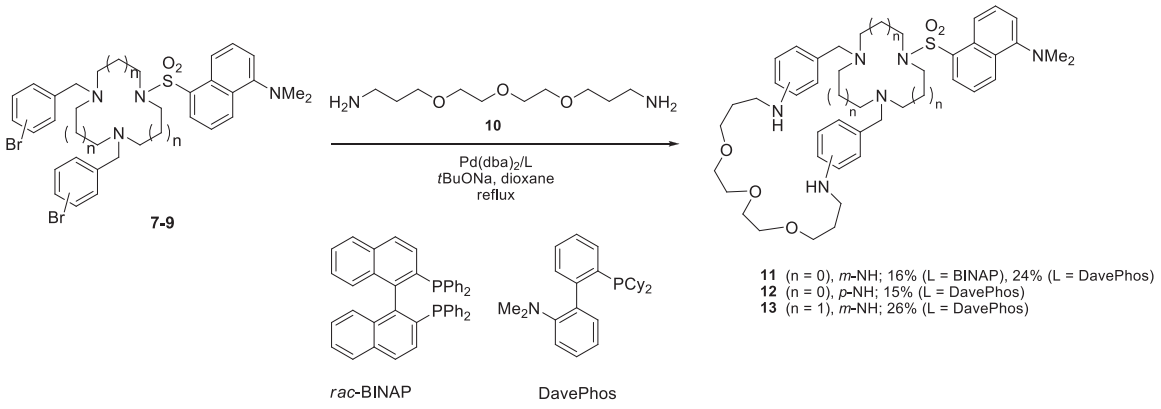


Scheme 1.

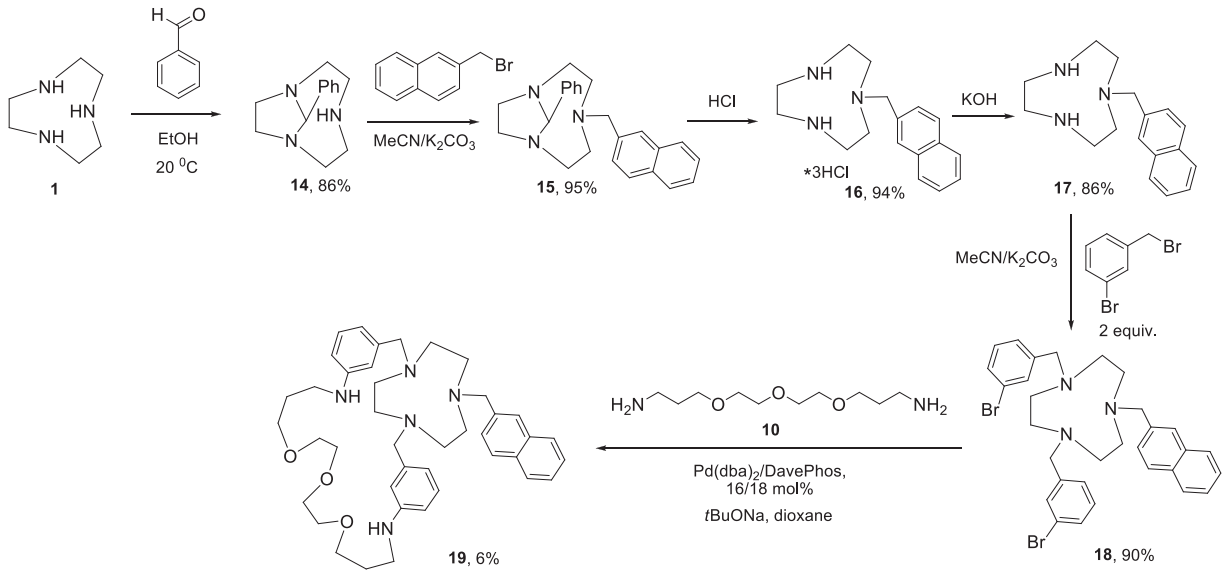
broadened. The attempt to sharpen the signals by a change of $CDCl_3$ for DMSO-d_6 leads to even more broadening of all signals at 298 K, but at 363 K some of them become narrow, however it is insufficient to obtain fully resolved signals for all protons. These facts can be explained by high-energy conformational transitions in these bicyclic compounds which were not observed for previously obtained macrobicycles based on dibenzyl substituted diazacrown ethers,[21] cyclen or cyclam[22] but were noted for the derivatives of tetrabenzyl substituted cyclen and cyclam.[23]

The approach which was found to be useful for the introduction of one dansyl group in TACN molecule could not be applied for the modification of this triazacycle with other fluorophore groups like naphthalene and acridine. The reactions of TACN with various amounts of 2-(bromomethyl)- and 2-(chloromethyl)naphthalene (0.5–1 equiv.) yielded inseparable mixtures of mono-, di- and trisubstituted TACN. To overcome this difficulty, we tried the method of TACN functionalization using the aminal protecting group.[19] According to a described method a bicyclic compound **14** was obtained in a high yield by reacting free TACN with benzaldehyde (Scheme 3). The reaction of compound **14** with 1 equiv. 2-(bromomethyl)naphthalene under standard conditions gave compound **15** in 95 % yield. After treatment by HCl in water to remove the aminal protection and washing with chloroform, trihydrochloride form **16** was obtained in 94 % yield. Its neutralization with KOH and extraction with chloroform provided 86 % yield of the monosubstitued TACN **17**. Its reaction with 2 equiv. 3-bromobenzyl bromide proceeded smoothly affording trisubstituted TACN **18** (90 % yield), and the macrocyclization was carried out using trioxadiamine **10** in the presence of $Pd(dba)_2$/DavePhos system. The yield of the target bicycle **19** after preparative chromatography was however quite poor (6 %).

The possibility to carry out a multistep synthesis of the macrobicycle containing a fluorophore group which cannot be introduced directly gave grounds for the synthesis of the relative compound possessing another fluorophore, *i.e.* acridine. The reaction of bicyclic aminal **14** with 9-(bromomethyl)acridine unexpectedly resulted in the formation of a mixture of deprotected mono-, di- and trisubstituted derivatives **21**, **22** and **23** in which compounds **21** and **23** prevailed (Scheme 4). Surprisingly, the expected monoacridinyl derivative with the aminal protection **20** was observed



Scheme 2.

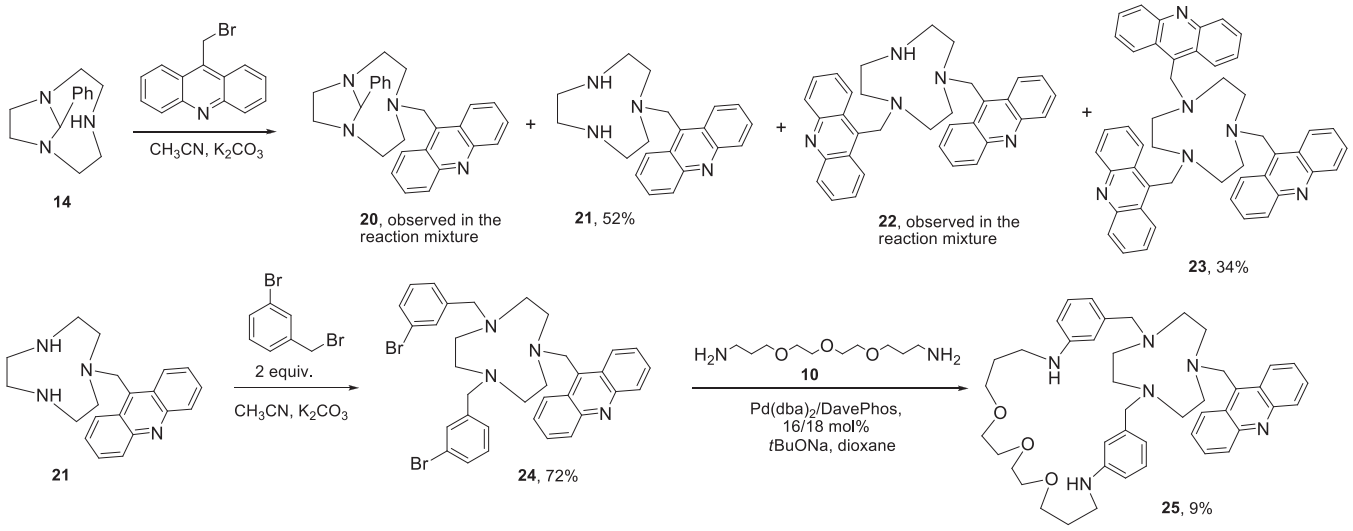


Scheme 3.

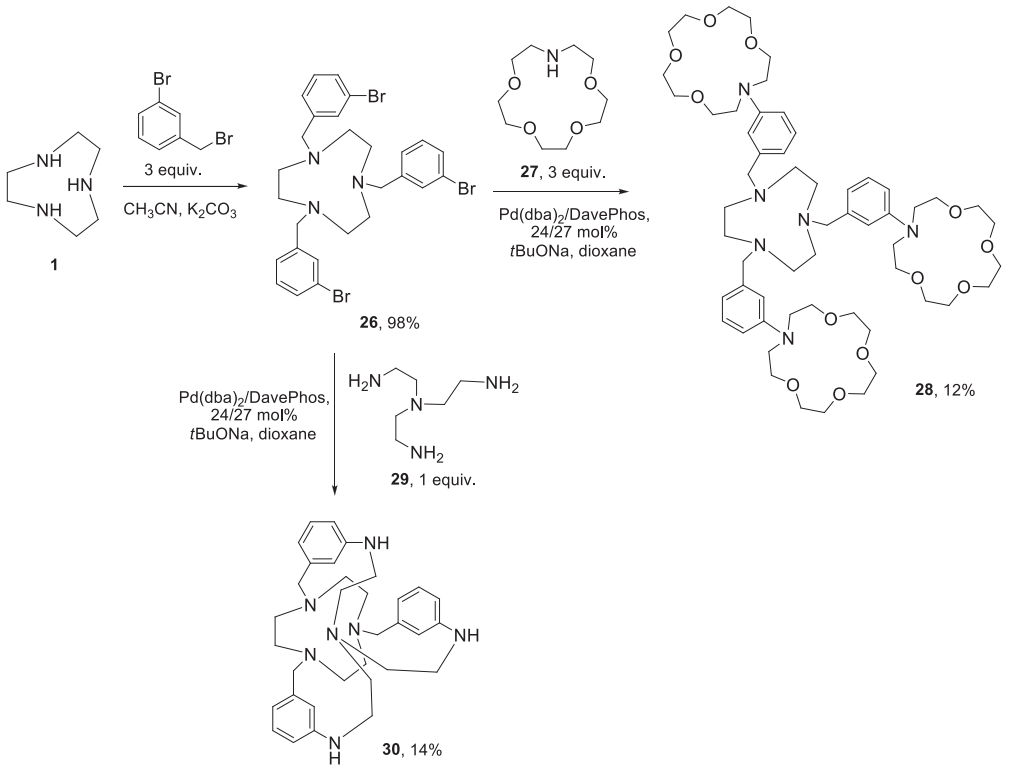
in the reaction mixture only in trace amounts (by *m/z*=409 $[M+H]^+$ in the MALDI-TOF spectrum and by a characteristic singlet at 5.65 ppm in the ^{1}H NMR spectrum which corresponds to CHN_2 proton). Chromatographic separation of the reaction mixture afforded compounds **21** and **23** in 52 and 34 % yields, respectively. The reaction of **21** with 2 equiv. 3-bromobenzyl bromide gave trisubstituted TACN derivative **24** in 72 % yield. The macrocyclization reaction of this compound with trioxadiamine **10** catalyzed by $Pd(dba)_2$/DavePhos system gave rise to the target macrocycle **25** in 9 %, however, it contained some admixtures which could not be separated by chromatography.

The ability of TACN to easily form trialkyl derivatives was employed in the synthesis of its *tris*(3-bromobenzyl) derivative **26** which was obtained in nearly quantitative yield (Scheme 5). The compound **26** was introduced in the Pd(0)-catalyzed amination with 3 equiv. 1-aza-15-crown-5 (**27**) in the presence of $Pd(dba)_2$/DavePhos system (8 mol% catalyst per each amino group), and desired tetramacrocyclic compound **28** was isolated in 12 % yield. The majority of starting compound was converted into bi- and tricyclic derivatives due to C-Br bond catalytic reduction. The compound **26** was shown to participate in the catalytic "end-capping" reaction with *tris*(2-aminoethyl)amine (**29**) which allowed the synthesis of a tetracyclic cryptand **30** in 14 % yield (Scheme 5).

The dansyl fluorophore group present in bicycles **11–13** is responsible for the absorption band at 340 nm



Scheme 4.



Scheme 5.

and intensive fluorescence at *ca* 520 nm. We investigated the possibilities of these compounds to work as fluorescent chemosensors for metal cations. In the course of investigation UV-Vis and fluorescent spectra of these compounds were recorded in MeCN in the presence of 1, 2, 5 equiv. of corresponding metal perchlorates or nitrates: Li(I), Na(I), K(I), Mg(II), Ca(II), Ba(II), Al(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), Ag(I), Pb(II) (perchlorates) and Ga(III), In(III), Y(III) (nitrates). The addition of 5 equiv. of corresponding cations to the cryptand **11** did not result in notable changes in the emission intensity except for Cu(II) and Al(III) which totally quenched fluorescence (Figure S1). These changes in fluorescence were accompanied with substantial changes in its UV-Vis spectra (Figure S2) as the addition of both metals led to disappearance of the absorption maximum at 305 nm and gave rise to a new maximum at 290 nm in the case of Al(III). Macrobicycles **12** and **13** were found to respond in a similar manner to the addition of 20 above mentioned metals (Figures S3 and S4) with almost total emission quenching in the presence of Al(III) and Cu(II). In the case of these cryptands we also noted 40–50 % reduction of the fluorescence intensity in the presence of 5 equiv. Ga(III) and In(III), as well as a slight emission enhancement in the presence of K(I) together with a small bathochromic shift of the maximum (from 520 to 513 nm). One may conclude that the emission quenching in the presence of Al(III) and Cu(II) is caused by the coordination with the dansyl fluorophore groups, probably *via* dimethylamino groups. There are literature data on a similar quenching of emission in dansylated azacrown ethers by Cu(II), Al(III) and Pb(II) cations.[24] We suppose that in the present case Pb(II) did not led to equal diminishing in fluorescence intensity due to a different coordination mode with N and O atoms of the bicyclic structures.

Conclusions

To sum up, we developed the synthetic approach to previously unknown bicyclic derivatives of 1,4,7-triazacyclononane (TACN) and 1,5,9-triazacyclododecane (TACD) bearing dansyl, naphthalene and acridine fluorophore groups using Pd(0)-catalyzed amination reactions, demonstrated the possibility to use unprotected TACN and TACD in the synthesis of dansyl-substituted bicycles, obtained tetracyclic derivatives of TACN using its *tris*(3-bromobenzyl) derivative, and showed the possibility to use dansylated bicycles as fluorescent molecular probes for detecting Cu(II) and Al(III) cations.

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