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Multicomponent reactions of amino alcohols with CH_2O and dithiols in the synthesis of 1,3,5-dithiazepanes and macroheterocycles

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ABSTRACT

A series of new hydroxyl-substituted 1,3,5-dithiazepanes and *N,N′*-(2-hydroxyethyl)tetrathiadiazacycloalkanes were synthesized by the multicomponent reactions (MCRs) of amino alcohols with formaldehyde and α,ω-dithiols. The MCR with 1,2-dithiol proceeds via a (1+2+1)-cyclocondensation with selective formation of 1,3,5-dithiazepanes. Stereochemistry of the dithiazepane ring was determined by X-ray diffraction. The reaction with higher α,ω-dithiols (1,3-propane-, 1,4-butane-, 1,5-pentane-, 1,6-hexanedithiol and 2-[2-(2-sulfanyletoxy)ethoxy]-1-ethanethiol) yielded OH-substituted macroheterocycles as a result of (2+4+2)-cyclocondensation. The structure of the latter was determined by NMR spectroscopy, MALDI–TOF and electrospray ionization methods. The doubly charged ions like $[M+2H]^{2+}$ are found in the ESI spectra of the macrocycles.

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1. Introduction

Sulfur- and nitrogen-containing macrocycles, due to stereochemical features and the presence of heteroatoms in a molecule, are perspective complexons, extracting agents for heavy metals, ionophores,[1] bioregulators and agents for supramolecular structures.[2] Among existing methods for one-pot synthesis of macroheterocycles, an especially attractive route is the *cyclo*-coupling of two bifunctional monomers, containing different heteroatoms, performed by template synthesis[3] or catalysis.[4] In recent years macrocyclization strategies have successfully involved MCRs with participation of bifunctional monomers and aldehydes;[5] including the Ugi reaction in tandem with intermolecular [3+2]-cycloaddition as well as two-component multimolecular (2+2)-cyclocondensation.[6]

There are several examples of MCR of amines with CH_2O and α,ω-dithiols to give the 1,5,3-dithiazepanes,[7] and one example leading to sulfur- and nitrogen-containing macroheterocycles with an uracil fragment as a result of intramolecular heterocyclization at the NH_2-group of amines.[8]

We noticed that the MCR of amino alcohols with CH_2O and dithiols proceeds via an intra- or inter-molecular heterocyclization depending on the length of the hydrocarbon chain connecting two thiol groups in the initial α,ω-dithiols.

2. Results and discussion

In order to expand the aforementioned research, and further elaborate an efficient one-pot method for the synthesis of OH-substituted *S,N*-hetero and macrocycles, we examined MCR of amino alcohols (NH_2OH, $NH_2(CH_2)_mOH$, m=2,4) with formaldehyde and α,ω-dithiols $HS(CH_2)_nSH$ (n=2–6). The used amino alcohols opens up the possibility for further functionalization of hetero- and macro-cycles onto the hydroxyl-groups.

We have found that the multicomponent heterocyclization could be implemented at 20 °C by admixing α,ω-dithiol to an aqueous solution of CH_2O with subsequent introduction of a corresponding amino alcohol into the reaction mixture at ratio of the starting reagents equal to 1:2:1. Seven- or macrocyclic *N,S*-containing heterocycles are formed under the indicated conditions, depending on the structure of the initial α,ω-dithiols (Scheme 1).

Thus, reaction of 1,2-ethanedithiol **2**a with amino alcohols **1a**–**e** and CH_2O proceeds as intramolecular heterocyclization with the formation of 1,5,3-dithiazepan-3-ol (**3**a), 2-(1,5,3-dithiazepan-3-

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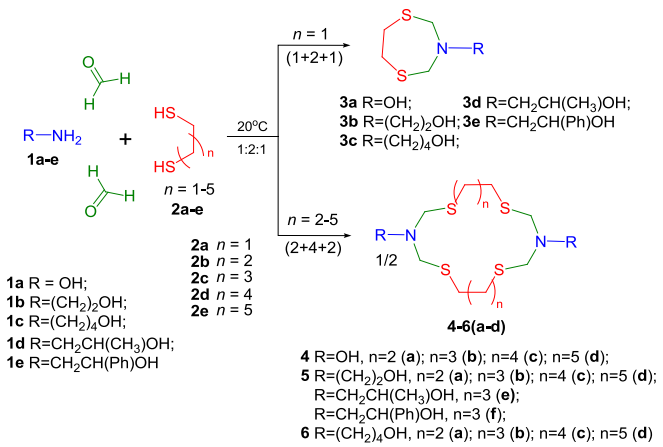
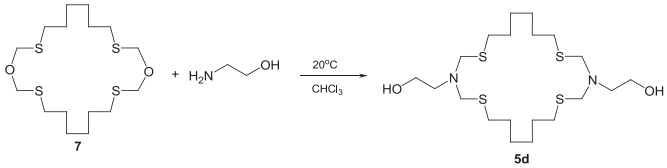


Scheme 1. Synthesis of 1,3,5-dithiazepanes and tetrathiadiazamacroheterocycles by MCR of amino alcohols with CH_2O and aliphatic α,ω-dithiols.

yl)-1-ethanol (**3b**) 4-(1,5,3-dithiazepan-3-yl)-1-butanol (**3c**), 1-(1,5,3-dithiazepan-3-yl)-2-propanol (**3d**), and 2-(1,5,3-dithiazepan-3-yl)-1-phenyl-1-ethanol (**3e**) with 90–98% yields (Scheme 1). Thus MCR of amino alcohols **1a**–**e**, CH_2O and 1,2-ethandithiols proceeds via an intramolecular type (1+2+1)-cyclocondensation. At the same time, the reaction of amino alcohols **1a**–**c** with CH_2O and α,ω-dithiols **2b**–**e**, having longer chains, proceeds as intermolecular condensation of two molecules of **1a**–**c**, four molecules of CH_2O and two molecules of **2b**–**e**, i.e., in accordance to three-component multimolecular (2+4+2)-cyclocondensation resulting in the formation of 16-, 18-, 20- and 22-membered tetrathiadiazamacrocycloalkanes **4** to **6a**–**d**, whose increase in size is accompanied by yield drop from 86 to 60%. Reaction of alkyl(-phenyl)substituted amino alcohols **1d**,**e** with CH_2O and α,ω-dithiols **2b**–**e** proceeds with the formation of product mixture, probably due to steric effects of the substituents.

It should be noted that upon interaction of amino alcohols **1a**–**c** with CH_2O and 1,6-hexandithiol **2**e, along with tetrathiadiazamacrocycloalkanes **4**–**6d**, 1,12-dioxa-3,10,14,21-tetrathiacyclodocozan (**7**) has also been isolated in an amount of about ~12%, wherein the latter forms as a consequence of intermolecular (2+4)-cyclocondensation of dithiol **2**e with CH_2O. Based on this fact one may assume that the reaction proceeds via the formation of intermediate dioxatetrathiamacrocycles, which are exposed in the reaction conditions to an action of amino alcohols with further formation of tetrathiadiazamacrocycloalkanes. In order to confirm that assumption, isolated from the reaction mixture 1,12-dioxa-3,10,14,21-tetrathiacyclododecosane (**7**) was reacted with 2-aminoethanol. As a result, the expected macroheterocycle **5d** was obtained, in accordance with (2+4+2)-cyclocondensation (Scheme 2).



Scheme 2. Synthesis of compound **5d**.

The ^{13}C NMR spectra of compounds **3a**–**c** show the two characteristic signals of C atoms of methylene groups $S(CH_2)_2S$ and NCH_2S in the regions δ_C 35.87–36.01 and δ 59.08–62.71, respectively. The resonance of the magnetically equivalent methylene protons in 1,3,5-dithiazepane ring appears in the ^1H NMR spectra as a two singlets in the regions δ_H 2.90–3.02 and δ_H 3.93–4.40, respectively, with an integrated intensity ratio of 1:1. On the basis of the data for compounds **3a**–**c** it is possible to propose a structure for the compound forming upon both (1+2+1) and (2+4+2) cyclocondensation processes, which would display similar sets of ^1H and ^{13}C NMR signals. Electron ionization (EI) mass spectrometry of the heterocycle **3b** shows a molecular ion peak $[M]^+$ at *m*/*z* 179. In MALDI TOF spectra for the compounds **3c**,**d** the presence of peaks $[M-H]^+$ is observed at *m*/*z* 206.356 and 192.270, respectively, whereas the same for the compound **3e** shows a molecular ion peak $[M+H]^+$ at *m*/*z* 256.247, which proves the formation of (1+2+1) cyclization products. For the compound **3a** a molecular ion in the mass spectra could not be registered, so the structure of **3a** was confirmed by X-ray diffraction (Fig. 1). Therefore taking into account the above-mentioned facts, the 1,5,3-dithiazepane structure can be attributed to the heterocycles **3a**–**e**.

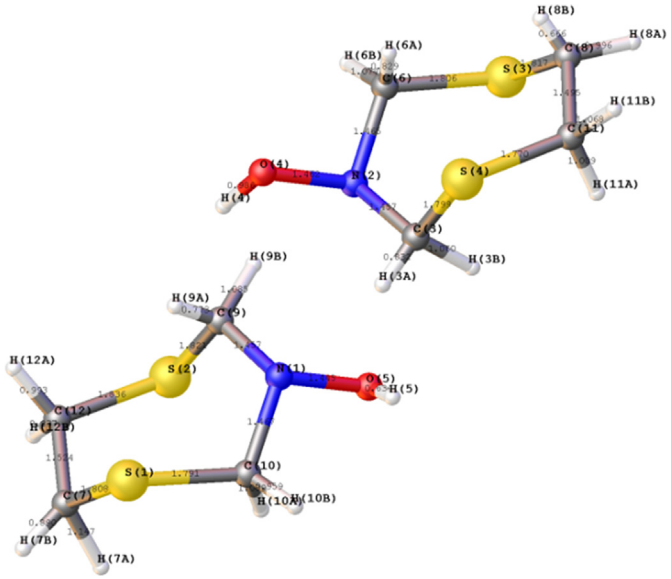


Fig. 1. Structure of two independent molecules **3a****A** and **3aB** according to the X-ray diffraction data.

X-ray diffraction analysis of compound **3a** demonstrates that the 1,3,5-dithiazepane fragment has a distorted *chair* conformation with atoms S(3) and S(4) transcending the C(8)C(11)C(3)C(6)N(2) plane by 1.086 Å and −1.112 Å, respectively. Lengths of the C–N bonds in the 1,5,3-diazepane fragment constitute 1.456 Å and 1.460 Å and correspond to simple C–N bonds. The length of the N–O bond constitutes 1.467 Å, which is much greater than that for simple N–O bonds. In heterocycle **3a** the hydroxyl group at a nitrogen atom occupies an axial position (anomeric effect). Such anomeric interaction of an unshared nitrogen atom N(1) pair (Lp) with antibonding σ^*_{C-S} orbitals of C–S bonds is characteristic for NCH_2S systems in 1,3,5-dithiazinans.[9]

Molecular packing for compound **3**a is represented by two diastereoisomers **3a****A** and **3aB** (Fig. 1). Bond angle C(3)–S(4)–C(11) for the first molecule constitutes 100.359°, whereas bond angle C(6)–S(3)–C(8) constitutes 101.019°. In the second molecule **3aB** bond angles C(7)–S(1)–C(10) and C(12)–S(2)–C(9) constitute 101.402° and 100.079°, respectively. Inclination angle of the hydroxyl group with regards to the ring plane comprises 78.865° in the first molecule and 82.252° in the second. The hydroxyl group is inclined towards atom C(10) by 1.813° more than towards atom C(9) in the first molecule, whereas in the second molecule the hydroxyl group inclination towards atom C(6) by 4.078° exceeds that towards atom C(3). Also, hydroxyl group protons of two

neighbouring molecules are oriented in opposite directions. In equivalence in constitutional parameters of diastereoisomers relates, probably, to a varying degree of crystallinity existing there between. Crystal structure is therefore stipulated by the existence of a stacking effect between the molecules.

Note that in the ^{1}H NMR spectra of the 1-(1,5,3-dithiazepan-3-yl)-2-propanol **3d** and the 2-(1,5,3-dithiazepan-3-yl)-1-phenyl-1-ethanol **3e**, methylene protons between the N and S atoms are magnetically nonequivalent, and their signals appears as doublets with geminal constant ^2J=14 Hz (Fig. 4, a), unlike narrow singlets in the series of compounds **3a**–c. It demonstrates a shift of the conformational equilibrium to a '*chair*–*chair*' conformation of the dithiazepane fragment in solution at room temperature (Fig. 2, a).

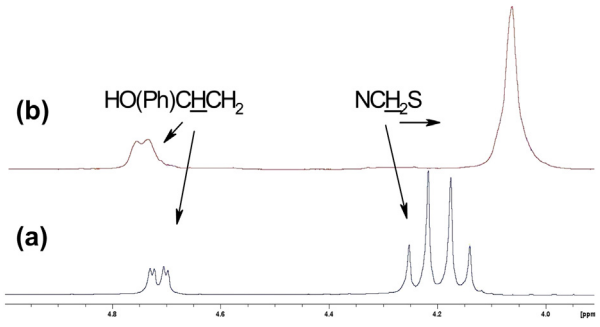


Fig. 2. The fragments ^{1}H NMR spectra of compounds **3e** (a) and **5f** (b).

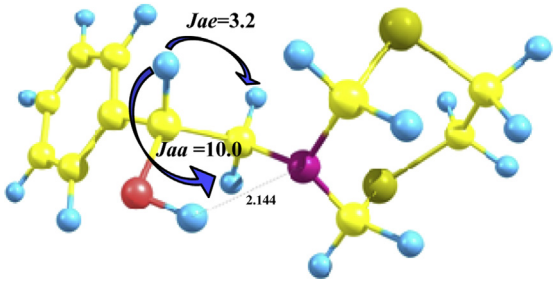


Fig. 3. Predominant conformer of compound **3e** (three-dimensional structure visualization performed by the program ChemCraft 1.6).[11]

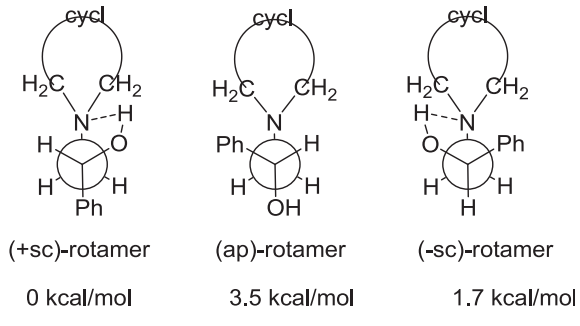


Fig. 4. Newman projection of the rotamers for compound **3e** and calculated relative values of Gibbs energy.

Moreover, we observed in the ^{1}H NMR spectrum of heterocycle **3e**, the doublet of doublets of the HO(Ph)C*H*CH$_2$ tertiary proton ($^3J_{aa}$=10.0 Hz, $^3J_{ae}$=3.2 Hz), which is indicative of the hindered rotation of the *N*-substituent due to hydrogen bonding (2.144 Å) between the nitrogen atom and a hydroxyl group N···H–O (Fig. 3), resulting in a five-membered pseudocycle. The value of spin–spin coupling constant ($^3J_{aa}$=10.0 Hz) indicated that the tertiary proton occupies a pseudoaxial location and the phenyl substituent adopts the equatorial position in the newly formed pseudocycle (Fig. 3). Indeed, this structure is the lowest conformer on the potential energy surface (PES) according to our calculations by PBE/3z (Priroda 6.0).[10]

The scanning of PES at rotation along the C_8–C_9 bond showed that there are three minima corresponding to three stable rotamers. The (+sc)-rotamer of compound **3e** with a five-membered pseudocyclic system corresponds the global minimum (Fig. 4).

By contrast, in the ^{1}H NMR spectrum of compound **5f**, the corresponding HO(Ph)C*H*CH$_2$ and NC*H*$_2$S protons appear as a multiplet at δ_H 4.73 and a broadened singlet at δ 4.06, due to more conformational flexibility (Fig. 2, b). Fig. 5 shows one of the stable conformers of 18-membered macrocycle **5f** with different conformational states of two SCH$_2$NCH$_2$S fragments, formed by (2+4+2)-cyclocondensation of the initial reagents.

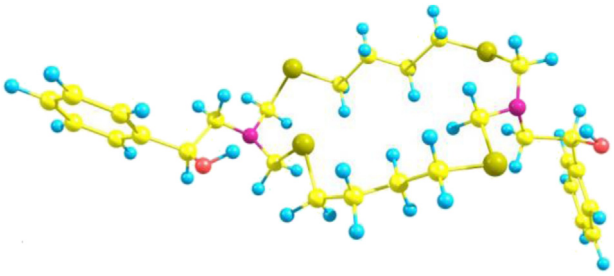


Fig. 5. Conformer of compound **5f** (three-dimensional geometric structure visualization performed by the program ChemCraft 1.6).[11]

Typically, in the ^{1}H and ^{13}C NMR spectra (CDCl$_3$, DMSO-d_6) of all macroheterocycles, the signals are shown as singlets due to the conformational mobility. For macroheterocycles **4** to **6a**–**d** analysis of one- and two-dimensional (COSY, HSQC, HMBC) spectra have shown that all signals with the expected chemical shifts were observed in the NMR spectra for each compound, and the ratio of integral intensities thereof in the ^{1}H NMR spectra corresponds to the suggested structures. Due to the molecules symmetry, in the ^{1}H and ^{13}C NMR spectra of the 16- and 18-membered macroheterocycles **4**–**6a**,**b** cyclic hydrogen and carbon atoms are observed as three resonance signals, and in the spectra of the 20- and 22-membered macroheterocycles **4**–**6c**,**d**—as four signals, respectively. Thus, signals for the ring atoms in compound **5b** in the ^{1}H NMR spectrum in DMSO-d_6 have the following chemical shifts: 1.60, 2.54 and 4.01 ppm; the intensity ratio is 1:1:1. In the HSQC spectrum these refer to signals δ_C 29.27, 31.07 and 57.40 ppm, respectively. The hydroxyethyl substituent, whose signals also are located in the middle region of the spectrum, was identified by characteristic cross-peaks in the COSY HH spectrum, observed between vicinal partners (vicinal J Spin–Spin Coupling Constants) in a N–C*H*$_2$–C*H*$_2$–OH fragment at δ_H 2.85, 3.62 ppm and δ_C 54.11 and 59.24 ppm. HMBC experimental data confirms the presence of a CH$_2$NCH$_2$SCH$_2$ fragment and the two types of CH$_2$NCH$_2$ fragments in the molecule (Fig. 6).

According to a NOE-diff experiment, the observed ^{1}H–^{1}H-interactions are indicative of a spatial closeness of the methylene protons NCH$_2$S with both *endo*- and with *exo*-cyclic protons.

As a result, methylene hydrogen and carbon atoms, localized in the macroheterocycles **4**–**6a**,**b** between atoms N and S, are observed as a singlet in the region δ_H 3.96–4.18 in the ^{1}H NMR spectra

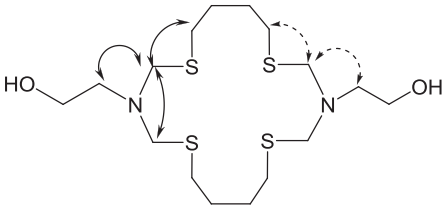


Fig. 6. The HMBC (plain lines) key correlations and the observed NOEs (dashed lines) for the macrocycle **5b** (protons are omitted for clarity).

and δ_C 56.82–59.82—in the ^{13}C NMR spectra. The other macroheterocycles were identified in similar manner.

Electrospray ionization (ESI) mass spectrometry indicated the formation of macroheterocycles **4a**–**d**, **5a**–**d** and **6a**–**d**. Peaks of varying intensity for molecular ions, formed due to addition of H^+-, Na^+-, K^+-cations and Cl^- anions, were registered. Except for compound **5a**, in all other cases low-intensity (0.5–6%) peaks of $[M+H]^+$ molecular ions were observed (**4b**–**d**). Abundant $[M+Na]^+$, $[M+K]^+$ molecular ions were registered only in the mass spectra of the compounds **5b**–**d**. Concerning ions $[M+Cl]^-$, observed in the mass spectra of macroheterocycles **4a**–**d**, **5**a,c and **6**c, it should be noted that those are formed primarily from the compounds having low gas phase acidity.[12] Such kinds of compounds give low-intensity mass spectrum peaks for $[M-H]^-$ ions or do not produce any peaks at all. Cl^- anions could possibly originate from the solvent since we have utilized a methanol/chloroform mixture in order to improve sample solubility. However, the presence of $[M+Cl]^-$ ions could be attributed also to contamination of the ion source.[12] Ions $[M+Cl]^-$ produce intense peaks in the mass spectra of compounds **4a**–**c**, **5a**, **5c** and **6c**. In case of compound **4d** the peak has low intensity (16%). In all other cases ions $[M+Cl]^-$ could not be observed.

A characteristic feature of the compounds **4a**–**d**, **5b**–**d** and **6a**–**d** is the formation of doubly charged $[M+2H]^{2+}$ ions under ESI conditions. At the same time, relative peak intensities for these ions in the mass spectra of all three groups of compounds differ one from the other. The most intense peaks for these ions (60–100%) are registered in the case of **5b**–**d**. In the mass spectra of compounds **4a**–**d** and **6a**–**d**, peak intensities for $[M+2H]^{2+}$ ions are approximately equal (Fig. 7). However, in the case of **6a**–**d**, peak intensities are varied for ions $[M+2H]^2$ from 12% to 31%.

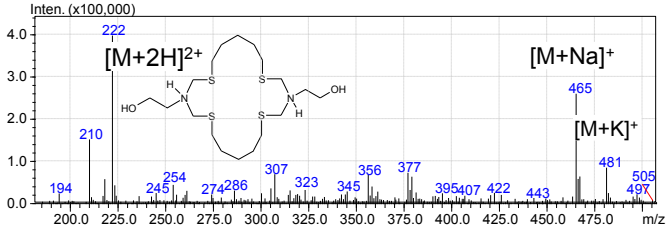
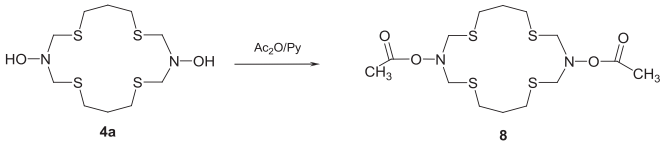


Fig. 7. ESI spectrum of the macrocycle **5**c.

The formation of complexes of macroheterocycles with cations, anions and H_2O is characteristic under conditions of chemical ionization in ESI mode; also known the is formation of doubly charged complexes with cyclic oligopeptides.[13] It should be noted that in case of compounds **4a**–**d**, the capability thereof to interact with two cations decreases along with an increase of macrocycle size. For products **5b**–**d** this capability is shown the greatest extent.[14]

Cryoscopic determination of the molecular weight of compound **4b** gives a value of 354±10.[15]

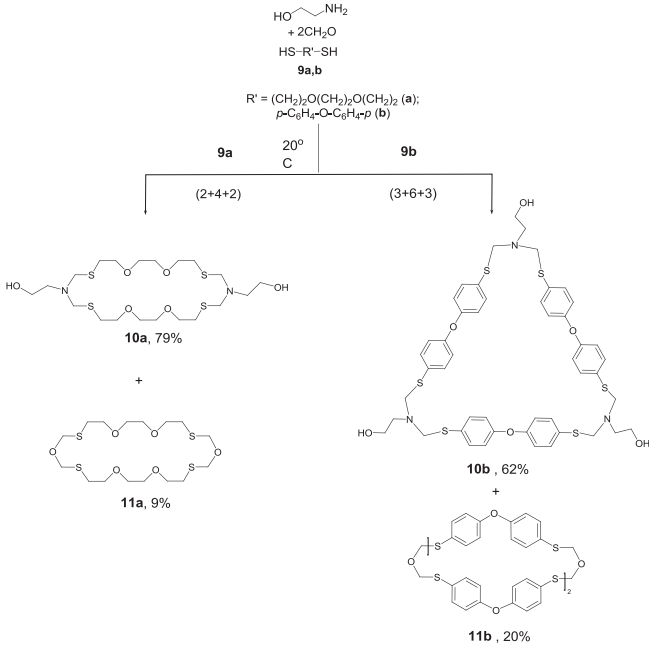
In order to confirm the structure of 1,5,9,13-tetrathia-3,11-diazacyclohexadecan-3,11-diol (**4**a) with greater reliability, acylation thereof by means of Ac_2O in pyridine solution has been carried out, resulting in the formation of 3,11-bis(acetoxy)-1,5,9,13-tetrathia-3,11-diazacyclohexadecan (**8**) (Scheme 3).



Scheme 3. Acylation of the compound **4**a.

In the ^1H and ^{13}C NMR spectra of product **8**, along with the signals for the methylene hydrogen and carbon atoms of the macrocycle (δ_H 1.91, 2.76 and 4.19 ppm and δ_C 29.39, 31.19 and 57.80 ppm), signals at δ_H 2.04 ppm and at δ_C 19.55, 168.80 ppm, corresponding to the acyl substituents, are present. Elemental analysis corresponds to a molecular formula of $C_{14}H_{26}O_4S_4N_2$, while the IR spectrum of compound **8** (film) exhibits intense bands at 1681 and 1759 cm^{-1}, which are indicative of the presence of a –C=O group and its enol form in the heterocyclic molecule. ESI mass spectrometry of product **8** contains a low-intensity peak at *m*/*z* 437, corresponding to the $[M+Na]^+$ ion. The data obtained are indicative of the formation of macroheterocycle **4**a upon condensation of muriatic hydroxylamine with formaldehyde and 1,3-propanedithiol.

To extend the application scope of the MCR occurring between primary amine alcohols, CH_2O and α,ω-dithiols, and to develop an efficient method to design macroheterocycles of varied structure, we have studied the reactivity of oxygen-containing dithiols, such as 3,6-dioxa-1,8-octandithiol **9**a and 4,4′-dimercaptodiphenyloxide **9b**. The reaction of **9a** with CH_2O and monoethanolamine gave 2-[19-(2-hydroxyethyl)-1,11,14,24-tetraoxa-4,8,17,21-tetrathia-6,19-diazacyclohexacozanyl] (**10a**) and 1,6,9,14,19,22-hexaoxa-3,12,16,25-tetrathiacyclohexacozan (**11**a) with yields 79 and 9%, respectively (Scheme 4).



Scheme 4. Synthesis of macroheterocycles by condensation of monoethanolamine with CH_2O and oxygen-containing dithiols.

It is essential to note that under selected conditions, 4,4′-dimercaptodiphenyloxide **9b**, comprising a conformationally 'rigid' diphenyloxide, reacts with CH_2O and monoethanolamine, giving a macroheterocycle **10b** (62%), constructed of three molecules of the monoethanolamine, six molecules of CH_2O and three molecules of dithiols, i.e., in accordance to (3+6+3)-cyclocondensation, as well as **11b** (20%), formed by cyclocondensation of dithiol **9b** with CH_2O.

Peaks for doubly charged ions were observed in the ESI mass spectrum of compound **10a**, those with maximal intensity correspond to ions $[M+2H]^{2+}$ at *m*/*z* 268 and $[M+2Na]^{2+}$ (19%) at *m*/*z* 290. Peaks for ions $[M+K]^+$ at *m*/*z* 573 (9%), $[M+Na]^+$ at *m*/*z* 557 (47%) and $[M+Cl]^-$ at *m*/*z* 569 (100%) were also observed.

MALDI–TOF spectra of the compounds **10b** and **11b** contain peaks at 981.919 and 909.357, which probably correspond to $[M+Na]^+$ and $[M+H_2O+K+Na]^+$ ions. The molecular ion $[M+H]^+$ for **11**a is observed in the MALDI–TOF spectrum at *m*/*z* 450.27 and in the atmospheric pressure chemical ionization (ESI) mass spectrum at *m*/*z* 450.

3. Conclusions

In summary, MCR of amine alcohols with formaldehyde and 1,2-ethanedithiol proceeds with the selective formation of OH-substituted 1,5,3-dithiazepanes in a (1+2+1)-cyclocondensation. It was shown that the reaction of aliphatic α,ω-dithiols (1,3-propane-, 1,4-butane-, 1,5-pentane-, 1,6-hexanedithiol and 2-[2-(2-sulfanyletoxy)ethoxy]-1-ethanethiol) with formaldehyde and amine alcohols allows gives products of intermolecular three-component (2+4+2)-cyclocondensation with the formation of novel *S*,*N*-macroheterocycles. Upon interaction of 4,4′-dimercaptodiphenyloxide with formaldehyde and monoethanolamine, a product of multimolecular (3+6+3)-cyclocondensation is formed. Thus, a novel, simple and efficient procedure for the preparation of *S*,*N*-macrocycles was demonstrated.

4. Experimental section

4.1. General

All reactions were performed at room temperature under air atmosphere in a round bottom flask equipped with magnetic stir bar. New compounds were characterized by ^1H (100.62 MHz), ^{13}C (400.13 MHz), ^1H–^1HCOSY, HSQC, HMBC, IR, GC–MS, LS-MS (APCI, ESI), MALDI–TOF, and elemental analysis. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer and referenced to 7.28 ppm and 77.10 ppm for chloroform, or to 2.50 ppm and 39.50 ppm for DMSO-d_6. IR spectra were recorded as thin films or from samples dispersed in mineral oil with a Bruker Vertex 70 v spectrometer. Electron ionization (70 eV) spectrum of compound **3b** was obtained on a Finnigan 4021 gas chromatography-mass spectrometer (HP-5 glass capillary column, 50,000×0.25 mm; carrier gas helium; oven temperature programming from 50 to 300 °C at a rate of 5 °/min; injector temperature 280 °C; ion source temperature 250 °C). Electron ionization (70 eV) spectrum of compound **3**c–**e** was obtained on a GCMS-QP2010 Ultra (Shimadzu) gas chromatography-mass spectrometer (Supelco 5 ms capillary column, 60,000×0.25; carrier gas helium; oven temperature programming from 40 °C to 150 °C at a rate of 10 °/min; injector temperature 260 °C; ion source temperature 200 °C). Atmospheric pressure chemical ionization (APCI) mass spectrum of the compound **5a** and electrospray ionization (ESI) mass spectra of the compounds **4**a–**d**, **5b**–**f**, **6**a–**d**, **7**, **8**, **10a**,**b** were obtained on a HPLC mass-spectrometer LCMS-2010EV (Shimadzu) in positive and negative ions mode at the corona discharge needle ionizing electrode and ionizing capillary potential of 4.5 kV and −3.5 kV, respectively. The temperature and voltage of the interface capillary under APCI (ESI) conditions was 230 °C and 5 (25) to −5 (−25) V, respectively. The nebulizer gas (nitrogen) flow rate was 0.5 (1.5) L/min. The high-frequency lenses (Q-array) voltage was 5 to −5 V. Sample solution (direct syringe sample inlet) under APCI (ESI) conditions was in methanol (acetonitrile), mobile phase was methanol (acetonitrile/water, 75/25). The mobile phase flow rate was 20 (50) μL/min. Mass spectra of the compound **3c**–**e** (in chloroform) and compounds **4a**, **5a**, **6c**, **7**, **10b**, **11a** and **11b** (in DMSO) were recorded on a spectrometer 'MALDI–TOF Autoflex III' (Bruker, Germany) with α-cyano-4-hydroxycinnamic acid as a matrix. Samples of the compounds were prepared by the 'dried droplet method' (1:10). The elemental analysis were determined on a Carlo Erba Model 1106 CHNS analyzer. The content of S in compounds **3c**, **4a**, **4b** and **5b** was determined by the Shenigers method.[15] The melting points were determined on an RNMK 80/2617 hot stage. Column chromatography was performed on silica gel. All starting amino alcohols and dithiols are commercially available.

All calculations were carried out using a program PRIRODA-06 developed by Laikov.[10,16] Geometric parameter optimization, vibrational frequency analysis, and calculation of entropy and thermodynamic corrections to the total energy of the compounds were carried out on the DFT level with the Perdew–Burke–Ernzerhof (PBE) functional in combination with a 3ζ basis set.[17] Thermodynamic parameters and activation energies were determined at 298 K. The minima were confirmed through the calculation of the force constant (Hessian) matrix and the analysis of the resulting frequencies. Visualization of quantum chemical data was carried out with the programs ChemCraft.[18]

4.2. Preparation of 1,5,3-dithiazepanes 3a–e and macroheterocycles 4a–d, 5a–f, 6a–d and 10a,b

Dithiol **2a**–**e** or **9a**,**b** (1 mmol) was mixed with a 37% solution of formaldehyde (0.15 mL, 2 mmol), and ethanol (3 mL) at room temperature over a period of 20 min. A solution of 0.07 g (1 mmol) of hydroxylamine hydrochloride **1a** in water (3 mL) was added to the reaction mixture and the mixture was stirred for 3–4 h at room temperature. The product obtained from hydroxylamine hydrochloride was neutralized with a 10% solution of NaOH. White precipitate that formed was filtered off and washed with H_2O (3*15 mL) then dried. The corresponding amino alcohol **1b**–**e** (1 mmol) in $CHCl_3$ (15 mL) was added dropwise to the reaction mixture and the mixture was stirred for 3–4 h at room temperature. The water was removed and the solution was dried with anhydrous $MgSO_4$. Solvent was removed, and the crude product was separated by column chromatography to give a pure sample **3a**–**e**, **5a**–**f** and **6a**–**d**, which was analyzed by NMR spectroscopy. The precipitate that formed from dithiol **2b**–**e** and hydroxylamine hydrochloride **1a** was filtered off, then was washed with water and dried. The product was washed with $CHCl_3$ and dried. The details of further purification performed for the new compounds are described in Product Data.

*4.2.1. 1,5,3-Dithiazepan-3-ol (**3**a).* White solid, yield 0.15 g (98%), R_f 0.74 (hexane/ethyl acetate/chloroform, 1:4:1); mp 94–95 °C (94–95 °C)[7a]; δ_H (400 MHz, $CDCl_3$, 25 °C) 3.02 (4H, s, SCH_2), 4.40 (4H, s, NCH_2), 6.67 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 36.0 (SCH_2), 62.7 (NCH_2).

*4.2.2. 8-(1,5,3-Dithiazepan-3-yl)-9-ethanol (**3b**).* Colourless oil, yield 0.33 g (93%), R_f 0.67 (CH_2Cl_2/1,4-dioxane, 10:1); ν_{max} (liquid film) 677 (C–S), 1051, 1273 (C–N), 1426, 2911, 3400 (OH) cm^{-1}. δ_H (400 MHz, $CDCl_3$, 25 °C) 2.70 (2H, t, *J* 5.2, NCH_2CH$_2$), 2.90 (4H, s,

SCH_2CH_2), 3.49 (2H, t, *J* 5.2, HOCH_2CH$_2$), 4.05 (1H, s, *H*O), 3.93 (4H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 35.9 (SCH$_2$CH$_2$), 53.1 (NCH$_2$CH$_2$), 58.7 (HOCH$_2$CH$_2$), 59.4 (NCH$_2$S); *m*/*z* (%): 179 (30) $[M]^+$, 148 (30) $[M-CH_2OH]^+$, 105 (15) $[SCH_2CH_2SCH_2]^+$, 42 (100) $[CHCH_2N]^+$. Anal. Calcd for $C_6H_{13}NOS_2$: C, 40.19; H, 7.31; N, 7.81; S, 35.77. Found: C, 40.15; H, 7.55; N, 7.60; S, 35.48.

*4.2.3. 4-(1,5,3-Dithiazepan-3-yl)-1-butanol (**3c**).* Colourless oil, yield 0.37 g (96%), R_f 0.80 (hexane/ethyl acetate/chloroform, 1:4:1); ν_{max} (liquid film) 675 (C–S), 1067, 1273 (C–N), 1427, 2934, 3367 (OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.50–1.58 (4H, m, NCH$_2$CH_2CH_2); 2.64 (2H, t, *J* 6.6, NCH_2CH$_2$); 2.98 (4H, s, SCH_2CH_2); 3.57 (2H, t, *J* 5.8, HOCH_2CH$_2$); 4.12 (4H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 23.9 (NCH$_2$CH$_2$); 30.8 (HOCH$_2$CH$_2$); 36.0 (SCH$_2$*C*H$_2$); 51.2 (NCH$_2$CH$_2$); 59.1 (NCH$_2$S); 62.4 (HOCH$_2$CH$_2$); *m*/*z* (%): 207 (10) $[M]^+$, 114 (100) $[M-SCH_2CH_2SH]^+$; MALDI TOF, *m*/*z*: 206.356 $[M-H]^+$. Anal. Calcd for $C_8H_{17}NOS_2$: C, 46.34; H, 8.26; N, 6.75; S, 30.93. Found: C, 46.56; H, 8.40; N, 6.90; S, 31.01.

*4.2.4. 1-(1,5,3-Dithiazepan-3-yl)-2-propanol (**3d**).* Colourless oil, yield 0.17 g (85%), R_f 0.70 (ethyl acetate/hexane/chloroform, 4:2:1). ν_{max} (liquid film) 678 (C–S), 1066, 1273 (C–N), 1449, 2911, 2966, 3421 (OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.11 (3H, d, *J* 6.4, Me); 2.27 (1H, dd, ^2J 13.2, $^3J_{aa}$ 10.0, NCH$_a$H$_b$CH); 2.89 (1H, dd, ^2J 13.2, $^3J_{ae}$ 2.8, NCH$_a$H$_b$CH); 2.94–3.05 (4H, m, SCH_2CH_2); 3.77 (1H, ddd, ^3J 10.0, ^3J 6.8, ^3J 2.8, C*H*Me); 4.09 (2H, d, ^2J 14.0, NCH_aS); 4.15 (2H, d, ^2J 14.0, NCH_bS); δ_C (100 MHz, $CDCl_3$) 21.2 (Me); 37.0 (SCH$_2$CH$_2$); 60.21 (*C*HMe); 60.8 (NCH$_2$S); 64.4 (NCH$_2$CH). *m*/*z* (%): 193 (36) $[M]^+$, 148 (71) $[M-CH(CH_3)OH]^+$, 100 (100) $[M-(CH_2S)_2]^+$, 42 (100) $[CHCH_2N]^+$. MALDI TOF, *m*/*z*: 192.270 $[M-H]^+$. GC–MS (70 eV); Anal. Calcd for $C_7H_{15}NOS_2$: C, 43.49; H, 7.82; N, 7.24; S, 33.17. Found: C, 43.56; H, 7.94; N, 7.16; S, 33.09.

*4.2.5. 2-(1,5,3-Dithiazepan-3-yl)-1-phenyl-1-ethanol (**3e**).* Colourless oil, yield 0.24 g (92%), R_f 0.65 (ethyl acetate/hexane/chloroform, 4:2:1). ν_{max} (liquid film) 701 (C–S), 1097, 1273, 1427, 1665, 2912, 2966, 3436 (OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 2.56 (1H, dd, ^2J 13.4, $^3J_{aa}$ 9.8, NCH_aH$_b$CH), 2.96 (4H, s, SCH_2CH_2), 3.10 (1H, dd, ^2J 13.4, $^3J_{ae}$ 3.4, NCH$_a$*H*$_b$CH), 4.16 (2H, d, ^2J 14.0, NCH_aH$_b$S), 4.24 (2H, d, ^2J 14.0, NCH$_a$*H*$_b$S), 4.71 (1H, dd, ^3J_a 10.0, ^3J_e 3.2, HOC*H*Ph), 7.25–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 36.9 (SCH$_2$CH$_2$), 60.6 (NCH$_2$CH), 60.7 (NCH$_2$S), 70.9 (HOCHPh), 127.0, 129.0, 129.5, 142.9 (CH^{Ph}); *m*/*z* (%): 163 [HOCH(Ph)CH$_2$N(CH$_2$)$_2$], 148 [CH$_2$N(CH$_2$SCH$_2$)$_2$], 134 [N(CH$_2$SCH$_2$)$_2$]; no molecular ion peak was observed. MALDI TOF, *m*/*z*: 256.247 $[M+H]^+$; ESI (70 eV); *m*/*z* (%): 256 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{17}NOS_2$: C, 56.43; H, 6.71; N, 5.48. Found: C, 56.47; H, 6.68; N, 5.54.

*4.2.6. 1,5,9,13-Tetrathia-3,11-diazacyclohexadecane-3,11-diol (**4a**).* White solid, yield (0.16 g) 96%, mp 140–142 °C. ν_{max} (Nujol) 722 (C–S), 1246, 3200 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 25 °C) 1.83 (4H; p, ^3J 7.2, CH$_2$CH_2CH$_2$), 2.75 (8H, t, ^3J 7.2, SCH_2CH$_2$), 4.18 (8H, s, NCH_2S); δ_C (100 MHz, DMSO-d_6) 29.8 (CH$_2$CH$_2$CH$_2$), 31.5 (SCH$_2$CH$_2$), 59.8 (NCH$_2$S). MALDI TOF, *m*/*z*: 329.384 $[M-H]^+$ (calcd for $C_{10}H_{21}N_2O_2S_4$, 329.550). ESI, (70 eV); *m*/*z* (%): 367 (51%) $[M+Cl]^-$; 365 (100) $[M]^+$, 166 (37) $[M+2H]^{2+}$. Anal. Calcd for $C_{10}H_{22}N_2O_2S_4$: C, 36.33; H, 6.71; N, 8.47; S, 38.80. Found: C, 36.36; H, 6.75; N, 8.54; S, 38.73.

*4.2.7. 1,5,10,14-Tetrathia-3,12-diazacyclooctadecane-3,12-diol (**4b**).* White solid, yield (0.10 g) 67%, mp 103–104 °C. ν_{max} (Nujol) 724 (C–S), 1110, 3326 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 25 °C) 1.62 (8H, br s, SCH$_2$CH_2), 2.63 (8H, br s, SCH_2CH$_2$), 4.02 (8H, s, NCH_2S); δ_C (100 MHz, DMSO-d_6) 29.0 (SCH$_2$CH$_2$), 31.9 (SCH$_2$CH$_2$), 59.8 (NCH$_2$S). ESI (70 eV); *m*/*z* (%): 393 (71) $[M+Cl]^-$, 359 (5) $[M+H]^+$; 180 (20) $[M+2H]^{2+}$; M_{cr}=354±10.[19] Anal. Calcd for $C_{12}H_{26}N_2O_2S_4$: C, 40.19; H, 7.31; N, 7.81; S, 35.77. Found: C, 40.26; H, 7.11; N, 7.85; S, 35.85.

*4.2.8. 1,5,11,15-Tetrathia-3,13-diazacycloicozane-3,13-diol (**4c**).* White solid, yield (0.15 g) 76%, mp 111–112 °C. ν_{max} (Nujol) 666 (–C–S–), 1179 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 25 °C) 1.40 (4H, br s, S(CH$_2$)$_2$CH_2), 1.54 (8H, br s, SCH$_2$CH_2), 2.63 (8H, br s, SCH_2CH$_2$), 4.07 (8H, s, NCH_2S); δ_C (100 MHz, DMSO-d_6) 27.9 (S(CH$_2$)$_2$CH$_2$), 29.4 (SCH$_2$CH$_2$), 32.4 (SCH$_2$CH$_2$), 59.7 (NCH$_2$S). ESI (70 eV); *m*/*z* (%): 421 (100) $[M+Cl]^-$, 387 (6) $[M+H]^+$, 194 (6) $[M+2H]^{2+}$. Anal. Calcd for $C_{14}H_{30}N_2O_2S_4$: C, 43.49; H, 7.82; N, 7.24; S, 33.17. Found: C, 43.52; H, 7.71; N, 7.25; S, 33.53.

*4.2.9. 1,5,12,16-Tetrathia-3,14-diazacyclodocozane-3,14-diol (**4d**).* White solid, yield (0.17 g) 83%, mp 90–93 °C. ν_{max} (Nujol) 722 (C–S), 1077 (C–N) cm^{-1}; δ_H (400 MHz, DMSO-d_6, 25 °C) 1.33 (8H, br s, S(CH$_2$)$_2$CH_2), 1.53 (8H, br s, SCH$_2$CH_2), 2.61 (8H, t, ^3J 7.2, SCH_2CH$_2$), 4.02 (8H, s, NCH_2S); δ_C (100 MHz, DMSO-d_6) 28.32 (S(CH$_2$)$_2$CH$_2$), 29.8 (SCH$_2$CH$_2$), 32.3 (SCH$_2$CH$_2$), 59.8 (NCH$_2$S). ESI (70 eV); *m*/*z* (%): 449 (16) $[M+Cl]^-$, 453 (8) $[M+K]^+$, 455 (6); $[M+Na]^+$, 208 (3) $[M+2H]^{2+}$. Anal. Calcd for $C_{16}H_{34}N_2O_2S_4$: C, 46.34; H, 8.26; N, 6.75; S, 30.93. Found: C, 46.26; H, 8.11; N, 6.62; S, 30.92.

*4.2.10. 2-[11-(2-Hydroxyethyl)-1,5,9,13-tetrathia-3,11-diazacyclohexadecanyl]-1-ethanol (**5**a).* Colourless oil, yield (0.16 g) 82%, R_f 0.72 (CH_2Cl_2/EtOH, 5:1). ν_{max} (liquid film) 666 (–C–S–), 1096, 1456, 2927 (–OH); δ_H (400 MHz, $CDCl_3$, 25 °C) 1.77 (4H, m, SCH$_2$CH_2), 2.57 (8H, m, SCH_2CH$_2$), 2.76 (4H, t, ^3J 5.4, HOCH_2), 3.54 (4H, t, ^3J 5.4, NCH_2CH$_2$), 3.96 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 29.9 (SCH$_2$CH$_2$), 30.3 (SCH$_2$CH$_2$), 53.6 (HOCH$_2$); 56.9 (NCH$_2$S), 59.0 (NCH$_2$CH$_2$); δ_H (400 MHz, DMSO-d_6, 25 °C) 1.60 (4H, m, SCH$_2$CH_2), 2.54 (8H, m, SCH_2CH$_2$), 2.70 (4H, t, ^3J 5.4, HOCH_2), 3.47 (4H, t, ^3J 5.4, NCH_2CH$_2$), 4.01 (8H, s, CH$_2$, NCH_2S); δ_C (100 MHz, DMSO-d_6) 29.3 (SCH$_2$CH$_2$), 31.1 (SCH$_2$CH$_2$), 53.8 (HOCH$_2$), 57.4 (NCH$_2$S), 59.8 (NCH$_2$CH$_2$). MALDI TOF, *m*/*z*: 386.414 $[M]^+$. APCI (70 eV); *m*/*z* (%): 421 (100) $[M+Cl]^-$, 387 (41) $[M+H]^+$. Anal. Calcd for $C_{14}H_{30}N_2O_2S_4$: C, 43.49; H, 7.82; N, 7.24; S, 33.17. Found: C, 43.23; H, 7.81; N, 7.29; S, 33.50.

*4.2.11. 2-[12-(2-Hydroxyethyl)-1,5,1,14-tetrathia-3,12-diazacyclooctadecanyl]-1-ethanol (**5b**).* Colourless oil, yield (0.16 g) 77%, R_f 0.65 (CH_2Cl_2/EtOH, 5:1). ν_{max} (liquid film) 662 (–C–S–), 1050, 1436, 2925; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.67 (8H, s, SCH$_2$CH_2), 2.66 (8H, s, SCH_2CH$_2$), 2.85 (4H, t, ^3J 5.4, HOCH_2), 3.62 (4H, t, ^3J 5.4, NCH_2CH$_2$), 4.03 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 29.1 (SCH$_2$CH$_2$), 31.6 (SCH$_2$CH$_2$), 54.1 (HOCH$_2$), 57.1 (NCH$_2$S), 59.2 (NCH$_2$CH$_2$); ESI (70 eV); *m*/*z* (%): 437 (22) $[M+Na]^+$, 208 (60) $[M+2H]^{2+}$. Anal. Calcd for $C_{16}H_{34}N_2O_2S_4$: C, 46.34; H, 8.26; N, 6.75; S, 30.93. Found: C, 46.40; H, 8.60; N, 7.00; S, 30.86.

*4.2.12. 2-[13-(2-Hydroxyethyl)-1,5,11,15-tetrathia-3,13-diazacycloicosanyl]-1-ethanol (**5c**).* Colourless oil, yield (0.15 g) 68%, R_f 0.27 (C_6H_{14}/CH_3CO_2Et/EtOH, 1:4:0.5). ν_{max} (liquid film) 665 (–C–S–), 1049, 1435, 3436 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.46 (4H, m, S(CH$_2$)$_2$CH_2); 1.58 (8H, m, SCH$_2$CH_2); 2.54 (8H, t, SCH_2CH$_2$); 2.85 (4H, t, ^3J 5.4, HOCH_2); 3.62 (4H, t, ^3J 5.4, NCH_2CH$_2$); 4.02 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 28.1 (S(CH$_2$)$_2$CH$_2$); 29.6 (SCH$_2$CH$_2$); 31.9 (SCH$_2$CH$_2$); 54.1 (HOCH$_2$); 57.2 (NCH$_2$S); 59.2 (NCH$_2$CH$_2$); ESI (70 eV); *m*/*z* (%): 477 (100) $[M+Cl]^-$, 481 (23) $[M+K]^+$, 465 (73) $[M+Na]^+$, 222 (100) $[M+2H]^{2+}$. Anal. Calcd for $C_{18}H_{38}N_2O_2S_4$: C, 48.83; H, 8.65; N, 6.33; S, 28.97. Found: C, 48.84; H, 8.56; N, 6.35; S, 29.02.

*4.2.13. 2-[14-(2-Hydroxyethyl)-1,5,12,16-tetrathia-3,14-diazacyclododecosanyl]-1-ethanol (**5d**).* Colourless oil, yield (0.14 g) 60%, R_f 0.44 (C_6H_{14}/CH_3CO_2Et/EtOH, 3:3:1). ν_{max} (liquid film) 665

(–C–S–), 1040, 1455, 3401 cm^{-1} δ_H (400 MHz, $CDCl_3$, 25 °C) 1.36 (8H, br s, $S(CH_2)_2CH_2$); 1.56 (8H, m, SCH_2CH_2); 2.53 (8H, t, SCH_2CH_2); 2.84 (4H, t, ^3J 5.4, $HOCH_2$); 3.61 (4H, t, ^3J 5.4, NCH_2CH_2); 4.01 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 28.4 ($S(CH_2)_2CH_2$); 29.9 (SCH_2CH_2); 32.0 (SCH_2CH_2); 54.1 ($HOCH_2$); 57.2 (NCH_2S); 59.1 (NCH_2CH_2); ESI (70 eV); *m/z* (%): 509 (36) $[M+K]^+$, 493 (59) $[M+Na]^+$, 236 (100) $[M+2H]^{2+}$. Anal. Calcd for $C_{20}H_{42}N_2O_2S_4$: C, 51.02; H, 8.99; N, 5.95; S, 27.24. Found: C, 51.05; H, 9.01; N, 6.03; S, 27.19.

*4.2.14. 1-[11-(2-Hydroxypropyl)-1,5,9,13-tetrathia-3,11-diazacyclohexadecanyl]-2-propanol (**5e**).* Colourless oil, yield (0.13 g) 62%, R_f 0.65 (ethyl acetate/hexane/chloroform, 4:2:1); ν_{max} (liquid film) 751 (C–S), 1059, 2926, 3426 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.00 (6H, d, *J* 6, Me), 1.62 (4H, m, $CH_2CH_2CH_2$), 2.28 (2H, m, NCH_aCH), 2.42 (8H, m, SCH_2CH_2), 2.50 (2H, m, NCH_bCH), 3.60 (2H, m, $CH_2CH(OH)CH_3$), 3.81 (8H, br s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 20.5 (Me), 30.1 ($CH_2CH_2CH_2$), 30.6 (SCH_2CH_2), 57.3 (NCH_2S), 59.8 (NCH_2CH), 64.0 ($CH_2CH(OH)CH_3$); ESI (70 eV); *m/z* (%): 208 (50) $[M+2H]^{2+}$. Anal. Calcd for $C_{16}H_{34}N_2O_2S_4$: C, 46.34; H, 8.26; N, 6.75; S, 30.93. Found: C, 46.40; H, 8.22; N, 6.71; S, 30.87.

*4.2.15. 2-[11-(2-Hydroxy-2-phenylethyl)-1,5,9,13-tetrathia-3,11-diazacyclohexadecanyl]-1-phenyl-1-ethanol (**5f**).* Colourless oil, yield (0.18 g) 68%, R_f 0.62 (Cl_4/2-propanols, 1:1); ν_{max} (liquid film) 701 (C–S), 1060, 1248, 1660, 3434 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.85 (4H, m, $CH_2CH_2CH_2$), 2.63 (8H, br s, SCH_2CH_2), 2.78 (2H, m, NCH_aCH), 2.97 (2H, m, NCH_bCH), 4.06 (8H, br s, NCH_2S), 4.73 (2H, m, $CH_2CH(OH)Ph$), 7.30-7.38 (10H, m, CH^{Ph}), δ_C (100 MHz, $CDCl_3$) 23.8 ($CH_2CH_2CH_2$), 31.2 (SCH_2CH_2), 57.8 (NCH_2S), 60.7 (NCH_2CH), 71.0 ($CH_2CH(OH)Ph$), 126.4 (CH^{Ph}), 128.1 (CH^{Ph}), 128.8 (CH^{Ph}), 142.2 (CH^{Ph}); ESI (70 eV); *m/z* (%): 270 (100) $[M+2H]^{2+}$. Anal. Calcd for $C_{26}H_{38}N_2O_2S_4$: C, 57.95; H, 7.11; N, 5.20; S, 23.80. Found: C, 57.89; H, 7.16; N, 5.26; S, 23.74.

*4.2.16. 4-[11-(4-Hydroxybutyl)-1,5,9,13-tetrathia-3,11-diazacyclohexadecanyl]-1-butanol (**6a**).* Colourless crystal, yield (0.14 g) 62%, mp 238–240 °C; ν_{max} (liquid film) 665 (C–S), 1062, 1244, 1434, 3367 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.53 (8H, br s, $NCH_2(CH_2)_2CH_2OH$), 1.81 (4H, pent, *J* 7.2, SCH_2CH_2), 2.57–2.65 (12H, m, SCH_2CH_2 and NCH_2CH_2), 3.57 (4H, s, $HOCH_2CH_2$), 3.97 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 24.0, 30.5, 51.5, 62.3 ($N(CH_2)_4OH$), 30.4 (SCH_2CH_2), 30.9 (SCH_2CH_2), 56.8 (NCH_2S); ESI (70 eV); *m/z* (%):222 (31) $[M+2H]^{2+}$. Anal. Calcd for $C_{18}H_{38}N_2O_2S_4$: C, 48.83; H, 8.65; N, 6.33; S, 28.97. Found: C, 48.85; H, 8.71; N, 6.36; S, 28.99.

*4.2.17. 4-[12-(4-Hydroxybutyl)-1,5,10,14-tetrathia-3,12-diazacyclooctadecanyl]-1-butanol (**6b**).* Colourless oil, yield (0.20 g) 86%; ν_{max} (liquid film) 649 (C–S), 1076, 1269, 1455, 3401 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.54 (8H, br s, $NCH_2(CH_2)_2CH_2OH$), 1.65 (8H, br s, SCH_2CH_2), 2.53 (8H, br s, SCH_2CH_2), 2.63 (4H, s, NCH_2CH_2), 3.58 (4H, s, $HOCH_2CH_2$), 3.97 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 24.1 (NCH_2CH_2), 29.2 (SCH_2CH_2), 30.6 ($HOCH_2CH_2$), 31.6 (SCH_2CH_2), 51.6 (NCH_2CH_2), 56.7 (NCH_2S), 62.3 (CH_2OH); ESI (70 eV); *m/z* (%): 236 (12) $[M+2H]^{2+}$. Anal. Calcd for $C_{20}H_{42}N_2O_2S_4$: C, 51.02; H, 8.99; N, 5.95; S, 27.24. Found: C, 50.98; H, 8.84; N, 5.96; S, 27.34.

*4.2.18. 4-[13-(4-Hydroxybutyl)-1,5,11,15-tetrathia-3,13-diazacycloicosanyl]-1-butanol (**6c**).* Colourless oil, yield (0.17 g) 67%, ν_{max} (liquid film) 756 (C–S), 1060, 1216, 3400 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.45 (4H, br s, $S(CH_2)_2CH_2$), 1.56 (16H, br s, SCH_2CH_2 and $NCH_2(CH_2)_2CH_2OH$), 2.52 (8H, br s, SCH_2CH_2), 2.63 (4H, s, $NCH_2(CH_2)_2CH_2OH$), 3.58 (4H, s, $HOCH_2$), 3.96 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 24.1 ($S(CH_2)_2CH_2$), 28.1 (NCH_2CH_2), 29.7 (SCH_2CH_2), 30.6 ($HOCH_2CH_2$), 31.9 (SCH_2CH_2), 51.6 (NCH_2CH_2), 56.7 (NCH_2S), 62.4 ($HOCH_2$); MALDI TOF, *m/z*: 250.112 $[M/2+H]^+$; ESI (70 eV); *m/z* (%): 533 (46) $[M+Cl]^-$, 497 (8) $[M-H]^-$, 250 (20) $[M+2H]^{2+}$. Anal. Calcd for $C_{22}H_{46}N_2O_2S_4$: C, 52.97; H, 9.29; N, 5.62; S, 25.71. Found: C, 53.02; H, 9.31; N, 5.56; S, 25.78.

*4.2.19. 2-[14-(2-Hydroxyethyl)-1,5,12,16-tetrathia-3,14-diazacyclodocosanyl]-1-ethanol (**6d**).* Colourless oil, yield (0.22 g) 83%; ν_{max} (liquid film) 650 (C–S), 1061, 1266, 1435, 3367 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.34 (8H, br s, $S(CH_2)_2CH_2$), 1.53 (16H, br s, SCH_2CH_2 and $NCH_2(CH_2)_2CH_2OH$), 2.50 (8H, t, ^3J 7.6, SCH_2CH_2), 2.64 (4H, s, ^3J 5.4, NCH_2CH_2), 3.56 (4H, t, $HOCH_2$), 3.95 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 24.5 ($S(CH_2)_2CH_2$), 28.4 (NCH_2CH_2), 30.0 (SCH_2CH_2), 30.6 ($HOCH_2CH_2$), 32.0 (SCH_2CH_2), 51.6 (NCH_2CH_2), 56.7 (NCH_2S), 62.4 ($HOCH_2$); ESI (70 eV); *m/z* (%): 675 (33) $[M+(CH_2)_6(SH)_2-H]^-$, 264 (14) $[M+2H]^{2+}$. Anal. Calcd for $C_{24}H_{50}N_2O_2S_4$: C, 54.70; H, 9.56; N, 5.32; S, 24.37. Found: C, 54.68; H, 9.57; N, 5.36; S, 24.42.

*4.2.20. 1,12-Dioxa-3,10,14,21-tetrathiacyclodocosane (**7**).* Compound **7** was obtained together with **5d** and isolated by column chromatography with (C_6H_{14}/CH_3CO_2Et/EtOH, 3:3:1) as the eluent. Colourless oil, yield (0.02 g) 12%, R_f 0.25; ν_{max} (liquid film) 655 (–S–C–), 1112, 1445 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.43 (8H, m, $S(CH_2)_2CH_2$), 1.66 (8H, m, SCH_2CH_2), 2.70 (8H, t, ^3J 7.6, SCH_2CH_2), 4.72 (8H, c, OCH_2S); δ_C (100 MHz, $CDCl_3$) 28.3 ($S(CH_2)_2CH_2$), 29.7 (SCH_2CH_2), 30.6 (SCH_2CH_2), 66.0 (OCH_2S); MALDI TOF, *m/z*: 384.204 $[M]^+$. Anal. Calcd for $C_{16}H_{32}O_2S_4$: C, 49.96; H, 8.38; S, 33.34. Found: C, 50.12; H, 8.35; S, 32.95.

*4.2.21. 3,11-Bis(acetyloxy)-1,5,9,13-tetrathia-3,11-diazacyclohexadecane (**8**).* A mixture of compound **4a** (0.1 g, 0.3 mmol) in pyridine (2 mL) and Ac_2O (1 mL) was stirred at room temperature during 24 h, then CH_2Cl_2 (5 mL) was added. The solution was washed by NH_4Cl (10%) (3*5 mL) and with water, then dried with Na_2CO_3. The solution was evaporated. Brown oil, yield (0.09 g) 73%, ν_{max} (liquid film) 650 (C–S), 1196, 1681 (–C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 1.91 (4H, t, ^3J 6.8, SCH_2CH_2), 2.04 (6H, s, Me), 2.76 (8H, t, ^3J 6.8, SCH_2CH_2), 4.19 (8H, s, NCH_2S); δ_C (100 MHz, $CDCl_3$) 19.6 (Me), 29.4 (SCH_2CH_2), 31.2 (SCH_2CH_2), 57.8 (NCH_2S), 168.8 (*C*OMe). Anal. Calcd for $C_{14}H_{26}N_2O_4S_4$: C, 40.55; H, 6.32; N, 6.76; S, 30.93. Found: C, 40.71; H, 6.26; N, 6.69; S, 30.90.

*4.2.22. 2-[19-(2-Hydroxyethyl)-1,11,14,24-tetraoxa-4,8,17,21-tetrathia-6,19-diazacyclohexacosanyl]-1-ethanol (**10a**).* Colourless oil, yield (0.21 g) 79%, R_f 0.68 (CH_2Cl_2/hexane/CH_3CO_2Et, 3:3:1); ν_{max} (liquid film) 754 (–C–S–C–), 1040, 1110, 3444 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 2.71 (8H, s, SCH_2CH_2), 2.83 (4H, t, NCH_2CH_2), 3.57 (8H, s, NCH_2S), 3.59 (8H, t, OCH_2CH_2O), 3.62 (4H, t, CH_2, $HOCH_2$), 4.08 (8H, s, OCH_2CH_2S); δ_C (100 MHz, $CDCl_3$) 31.0 (SCH_2CH_2), 54.0 (NCH_2CH_2), 57.5 (NCH_2S), 59.3 ($HOCH_2$), 70.2 (OCH_2CH_2S), 71.5 (OCH_2CH_2O); ESI (70 eV); *m/z* (%): 573 (9) $[M+K]^+$, 557 (47) $[M+Na]^+$, 290 (19) $[M+2Na]^{2+}$, 268 (100) $[M+2H]^{2+}$, 569 (100) $[M+Cl]^-$. Anal. Calcd for $C_{20}H_{42}N_2O_6S_4$: C, 44.91; H, 7.92; N, 5.24; S, 23.98. Found: C, 44.93; H, 7.85; N, 5.19; S, 24.04.

*4.2.23. 2-[18-(2-Hydroxyethyl)-11,25-dioxa-2,6,16,20-tetrathia-4,18-diazapentacyclo[24.2.2.2^{7,10}.2^{12,15}.2^{21,24}]hexatriaconta-1(28),7,9,12,14,21,23,26,29,31,33,35-dodecaen-4-yl]-1-ethanol (**10b**).* Colourless crystal, yield (0.19 g) 62%, mp 94–95 °C. R_f 0.40 (CH_2Cl_2/hexane/CH_3CO_2Et, 3:3:1:1); ν_{max} (Nujol) 750 (C–S), 1150, 1470 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 2.89 (6H, m, NCH_2CH_2), 3.46 (6H, m, CH_2CH_2OH), 4.41 (12H, s, NCH_2S), 4.99 (3H, br s, OH), 6.95 (12H, d, ^3J 6.8, Ph), 7.43 (12H, d, ^3J 6.8, Ph); δ_C (100 MHz, $CDCl_3$) 54.1 (NCH_2C), 58.7 (CH_2CH_2OH), 61.8 (NCH_2S), 119.7, 131.8, 134.5, 156.6 (Ph); MALDI TOF, *m/z*: 981.919 $[M+Na]^+$. Anal. Calcd for

$C_{48}H_{51}N_3S_6O_6$: C 60.16, H 5.36, N 4.38, S 20.08. Found: C 60.17, H 5.29, N 4.40, S 20.11.

*4.2.24. 1,6,9,14,19,22-Hexaoxa-3,12,16,25-tetrathiacyclohexacosane (**11**a).* Colourless oil, yield (0.02 g) 9%, R_f 0.43 (CH_2Cl_2/hexane/CH_3CO_2Et/EtOH, 3:3:1:1). ν_{max} (liquid film) 649 (–S–C–), 1109, 1455 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 2.69 (8H, m, SCH_2CH_2O), 3.55 (16H, m, SCH_2CH_2 and $O(CH_2)_2O$), 4.58 (8H, br s, OCH_2S); δ_C (100 MHz, $CDCl_3$) 32.5 (SCH_2CH_2), 67.2 (SCH_2CH_2), 69.7 ($O(CH_2)_2O$), 71.8 (OCH_2S); MALDI TOF, *m*/*z*: 450.27. ESI (70 eV); *m*/*z* (%): 484 (32) $[M+Cl]^-$, 450 (54) $[M+H]^+$, 448 $[M-H]^-$. Anal. Calcd for $C_{16}H_{32}O_6S_4$: C 42.83; H, 7.19; S, 28.59. Found: C 42.79; H, 7.23; S, 28.65.

*4.2.25. 4,11,18,25,32,39-Hexaoxa-2,6,16,20,30,34-hexathiaheptacyclo [38.2.2.2^{7,10}.2^{12,15}.2^{21,24}.2^{26,29}.2^{35,38}]tetrapentaconta-1(42),7(54),8,10 (53),12,14,21,23,26,28,35,37,40,43,45,47,49,51-octadecane (**11b**).* White solid, yield (0.06 g) 20%, mp 65–67 °C. R_f 0.15 (CH_2Cl_2/hexane/CH_3CO_2Et/EtOH, 3:3:1:1); ν_{max} (Nujol) 896, 1092, 1580, 3059 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 25 °C) 4.99 (12H, s, SCH_2O), 6.99 (12H, d, *J* 8.6, Ph), 7.51 (12H, d, *J* 8.6, Ph); δ_C (100 MHz, $CDCl_3$) 69.2 (SCH_2O), 119.6, 131.8, 133.4, 156.7 (C^{Ph}). MALDI TOF, *m*/*z*: 909.357 $[M+K+Na+H_2O]^+$. Anal. Calcd for $C_{42}H_{36}O_6S_6$: C 60.84; H, 4.38; S, 23.20. Found: C 60.89; H, 4.36; S, 23.11.

4.3. Crystal structure analysis of compound 3a

The 0.24×0.36×0.4 single crystal of **3a** was prepared by slow evaporation of a hexane/ethyl acetate/chloroform (1:4:1) solution at room temperature. X-ray diffraction data was collected on a XCalibur Eos diffractometer with graphite monochromated Mo-Kα radiation (λ=0.71073 Å). Collection and processing of data was performed using the program CrysAlis^{Pro} Oxford Diffraction Ltd., Version 1.171.33.66. The structure was solved by direct methods as implemented in the program SHELXS-97.[20] The refinement was carried out using SHELXL-97.[21] The structure was refined by a full-matrix least-square technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms.

Crystal structure data of **3a**: $C_4H_9NS_2O$, *M*=100.84, triclinic, P1 (no. 1), *a*=6.5991(7) Å, *b*=6.9097(7) Å, *c*=8.2602(9) Å, α=109.839(10)°, β=95.545(9)°, γ=94.714(8)°, *V*=349.97(7) Å^3, *T*=239.(2), D_{calcd}=1.4353 mg/mm^3, *Z*=3, reflections collected=5222, independent reflections=3814 (R_{int}=0.0196), final *R* index [I 2σ(I)]: R_1=0.035372; R index (all data): wR_2=0.1103. Crystallographic data for the structure of **3a** have been deposited in the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 948885. Copies of these data can be obtained free of change on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk) or from http://www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.053.

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