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Synthesis and reactivity of acyclic and macrocyclic uracils bridged with five-membered heterocycles

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ABSTRACT

Replacement of terminal atoms of Br in 1,3-bis(bromopentyl)-5(6)-substituted uracils with 2-mercapto-5-methyl-1,3,4-thiadiazole, 2,5-dimercapto-1,3,4-thiadiazole, 2-mercaptoimidazole, and 2-mercaptobenzimidazoles resulted in a series of acyclic compounds and isomeric heterocyclophanes. Structures of macrocyclic regioisomers were unambiguously determined by NMR data. One of the regioisomers exhibits a hypochromic effect with respect to model compounds. The acyclic uracils obtained bridged with five-membered heterocycles are alkylated with methyliodide and methyl tosylate, and oxidated with *m*-CPBA, H_2O_2, and I_2.

1. Introduction

Heterocyclic compounds and especially five-membered heterocycles with atoms of N, S, O in the ring exhibit a wide spectrum of biological activity. A great deal of relatively simple oxazolic, thiazolic, imidazolic structures have been synthesized, and their diverse physiological properties were established.[1–6] On the other hand derivatives of the five-membered heterocycles with three dimensional architecture are less well. Such derivatives considered as acyclic or macrocyclic compounds consist of a number of heterocycles bridged to each other with some kind of spacer. Our idea is to combine five-membered heterocyclic moieties with nucleotide bases and in particular with uracil fragments to develop compounds with an acyclic or macrocyclic topology. The main goal is to elaborate methods of preparation of such substituted uracils for their subsequent examination and especially for their biological activity screening.

Synthesis of acyclic and macrocyclic uracils and purines linked to each other with polymethylene spacer was well-documented in connection with photochemical and structural studies of the compounds.[7–13] Contrary, there are only few reports concerning nucleobases bridged with other heterocyclic five- or six-membered systems. In particular, thymine, cytosine, adenine, and guanine were tethered to indole,[14,15] benzimidazole,[16] aminoquinoline,[17] and aminoacridine[18–20] by $-(CH_2)_n-$chains (n=3–6). Those compounds were of great interest in the context of their hypochromism and fluorescence, and their ability to interact with native DNA as intercalators and DNA repair inhibitors.

Herein we have attempted to provide a method for preparing compounds, which consist of uracil derivatives and five-membered heterocycles bridged to each other with polymethylene chains. The starting materials for the introduction of uracilic constituents were 1,3-bis(ω-bromoalkyl)-5(6)-substituted uracils, in particular 1,3-bis(5-bromopentyl-1)-6-methyluracil (**1a**) and 1,3-bis(bromopentyl-1)-5-bromouracil (**1b**). For heterocyclic constituents mercapto-substituted five-membered heterocycles with atoms of N and S, namely 2-mercapto-5-methyl-1,3,4-thiadiazole (**2**), 2,5-dimercapto-1,3,4-thiadiazole (**3**), 2-mercaptoimidazole (**4**), 2-mercaptobenz- imidazole (**5a**), and 2-mercapto-5-nitrobenzimidazole (**5b**) were used. These heterocycles have been chosen, first of all, to vary the heteroatoms inside the ring and, secondly, to vary the reaction centers at the ring, especially the mercapto- and imide functions.

The combination of uracilic and heterocyclic moieties has been performed with a simple procedure using sodium hydride as a base and DMF as a solvent. Under these conditions acyclic and macrocyclic compounds with purine and uracil derivatives bridged to each other were previously prepared.[10,21]

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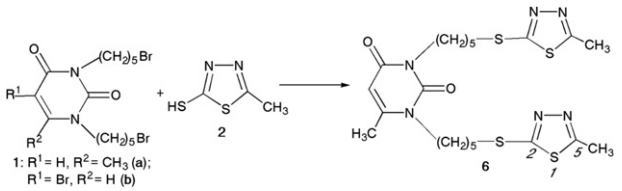
2. Results and discussion

2.1. Interaction of 1,3-bis(bromopentyl)-5(6)-substituted uracils with five-membered heterocycles

It is evident that if a heterocycle has a single reaction site there is no problem obtaining the products of substitution of both Br terminal atoms in dibromides **1a**,**b** with the heterocycle. In particular, the mercapto-group in thiadiazole derivative **2** is an unambiguous center for the attack of different reagents. In fact, the reaction of dibromide **1a** with heterocycle **2** at the ratio of **2**/NaH/**1a** 2:2:1 produced bissubstituted compound **6** with a good yield (Scheme 1). Signals of SCH_2-protons are disposed at 3.20–3.30 ppm, and this region is at a distance from other proton signals especially methylene groups at N^1 and N^3 of the pyrimidine ring (3.80–3.95 ppm). These features of spectra for compound **6** and other compounds with a similar structure, which are reported herein allow to identify them with comparative ease.

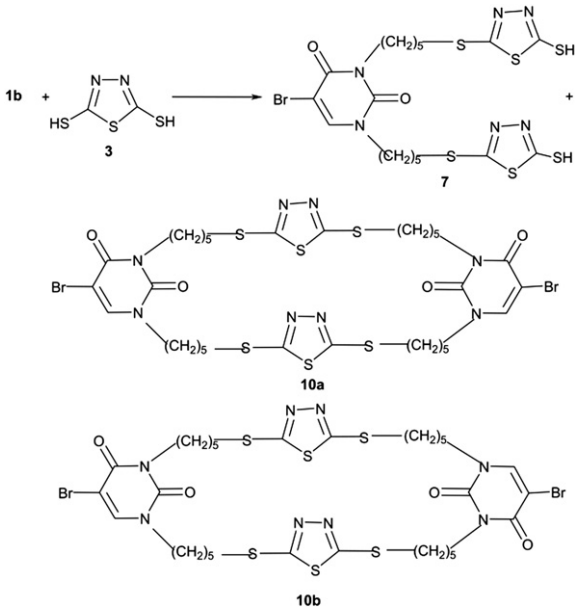


Scheme 1. Reagents and conditions: NaH, DMF, rt.

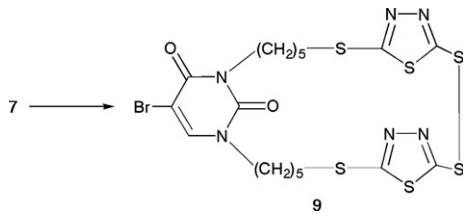
On the contrary, the occurrence of two reaction sites in a heterocycle significantly complicates the reaction of the heterocycle with dibromides **1a**,**b**. Particularly, in the mass-spectrum MALDI-TOF of the reaction mixture of dibromide **1b** with 2,5-dimercapto-1,3,4-thiadiazole **3**, in a ratio of **3**/NaH/**1b** 2:2:1, four peaks of molecular ions with *m*/*z* 477.0, 625.2, 626.1, and 954.6 were observed. In addition to the apparent acyclic dithiazole **7** with the calculated *m*/*z* 625.9 the other three molecular ions are assigned to macrocyclic structures **8** with one 5-bromouracil and one 2,5-dimercapto-1,3,4-thiadiazole moieties (calcd *m*/*z* 476.0), to **9** with one 5-bromouracil and two 2,5-dimercapto-1,3,4-thiadiazole moieties (calcd *m*/*z* 624.9), and to **10a**,**b** with two 5-bromuracil and two 2,5-dimercapto-1,3,4-thiadiazole moieties (calcd *m*/*z* 952.8). In fact, only products **7** and **10a**,**b** were successfully isolated from the reaction mixture (Scheme 2). Due to the asymmetry of the pyrimidine cycle, macrocycles **10a**,**b** are isomeric heterocyclophanes, isomeric macrocycles distinguished from one another by mutual arrangement, cis or trans of C_{ur}^4=O-group at pyrimidine rings. This phenomenon was described in detail in a series of pyrimidinophanes.[13,22,23] Individual *cis*- and *trans*-isomers **10a** and **10b** were not isolated, and the mixture of isomers was obtained. These compounds are the first case of isomerization in a series of macrocycles with uracil moieties, which contain heterocycle units.

Dithiazole **7** was oxidized to heterocyclophane **9** using triethylamine as a base (Scheme 3).[24] This shows that heterocyclophane **9** can be formed in the reaction of dibromide **1b** with heterocycle **3**, in particular as a result of air oxidation of the product **7**. It is assumed that the peak of *m*/*z* 625.2 in the mass-spectrum of the reaction mixture of the compounds **1b** and **3** corresponds to the macrocycle (calcd for $C_{18}H_{21}Br^{79}N_6O_2S_6$ $[M+H]^+$ 624.9).

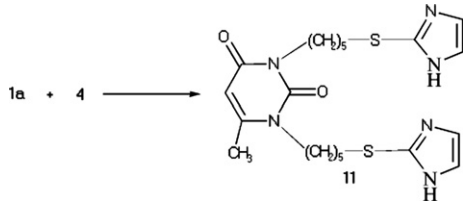
Imidazole **4** with two different reaction N and S centers smoothly reacts with dibromide **1a** affording compound **11** in satisfactory yield (Scheme 4). We failed to isolate other products, in particular compounds with bridged 6-methyluracil and imidazole moieties through the N atom of the five-membered heterocycle. However, it is evident that the reaction of the dibromides with



Scheme 2. Reagents and conditions: NaH, DMF, rt.



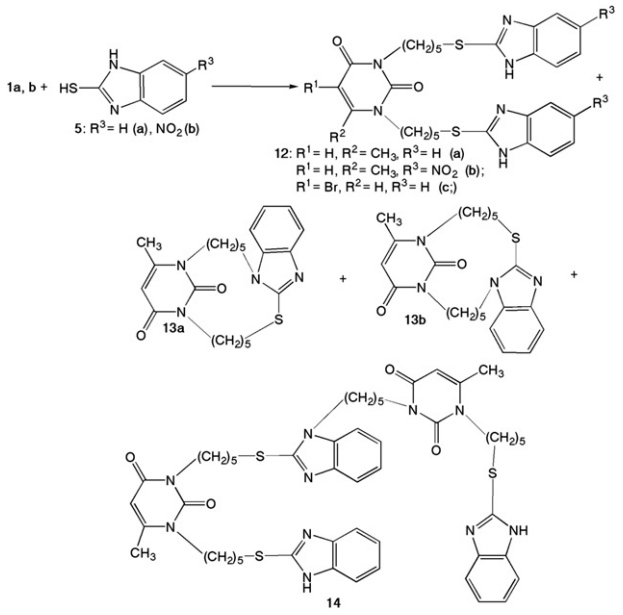
Scheme 3. Reagents and conditions: I_2, NEt_3, $CHCl_3/CH_3OH$, rt.



Scheme 4. Reagents and conditions: NaH, DMF, rt.

derivatives of heterocycle **4** should give both *S*- and *N*-substituted imidazoles.

Reactions of benzimidazole **5**a and 5-nitrosubstituted benzimidazole **5b** with dibromides **1a**,**b** at the ratio of **5a**,**b**/NaH/dibromide **1a**,**b** 2:2:1 produced bissubstituted uracils **12a**–**c** in 43–53% yields. Furthermore, it has been found that a series of side compounds were formed. Regioisomeric heterocyclophanes **13a**,**b**, both in a 2% yield, and oligomer **14** in a 3% yield were isolated in the case of the reaction of heterocycle **5a** with dibromide **1a** (Scheme 5). Directed preparation of the heterocyclophanes **13a**,**b** at the ratio of heterocycle/NaH/dibromide 1:2:1 increased the yields of the isomers up to 7%. However, at these conditions the amount of bissubstituted uracil **12a** was insignificant. The ratio of heterocycle/NaH/dibromide 2:4:1 gave compounds **12a**, **13a**,**b**, and **14** in yields 29, 5, 3, and 4%, respectively. Thus, the 2:2:1 ratio seems to be the optimal proportion for the reaction affording a series of the products with acceptable yields.



Scheme 5. Reagents and conditions: NaH, DMF, rt.

2.2. Structure elucidation of macrocyclic isomers 13a,b in solution

Heterocyclophanes **13a**,**b** are the cases of macrocycles in which a nucleotide base derivative, in particular uracil derivative is bridged with other five- or six-membered heterocycles. These macrocycles can be utilized as model compounds for exploring interactions between nucleotide bases and drug or protein fragments. Such an approach, especially was applied previously to elucidate interactions between nucleotide bases and tryptophan. For this purpose acyclic compounds 'base–$(CH_2)_3$–indole' were used.[14,15] From this point of view it is of interest to determine the mutual orientation of uracil and benzimidazole moieties in isomeric heterocyclophanes **13a**,**b**.

In general, due to a different bonding mode the combination of 6-methyluracil and 2-thiobenzimidazole moieties with two pentamethylene chains resulted in two regioisomers (Scheme 5 and Fig. 1). In one isomer the pentamethylene spacer binds N^1 of the uracil unit and the S atom of the benzimidazole moiety, and it is considered an *anti*-isomer with the *anti*-arrangement of $C_{ur}{}^4$=O and C_{imid}–S bonds. The other isomer with $N_{ur}{}^3(CH_2)_5$S-bridge and the *syn*-arrangement of $C_{ur}{}^4$=O and C_{imid}–S bonds is considered a *syn*-isomer. These macrocycles were isolated by column chromatography, and to distinguish them the regioisomers from first and second fractions of the eluate are labeled **A** and **B**, respectively.

^{1}H NMR spectra of the regioisomers **A** and **B** differ one from the other insignificantly, and there are no obvious indications to perform structural correlations. In addition, superposition of proton signals of both pentamethylene spacers in the ^{1}H NMR spectra of **A** and **B** makes elucidation of bonding mode of 6-methyluracil and 2-thiobenzimidazole moieties rather difficult. A variety of NMR correlation methods[25,26] were used to establish structures of the regioisomers **A** and **B**. First, combination of 2D ^{1}H–^{13}C HSQC and ^{1}H–^{15}N/^{13}C HMBC correlations allow to determine directly uracilic and benzimidazolic moieties, and Fig. 1 shows some of the experimental correlations for **A**. In ^{1}H NMR spectra of **A** and **B** there are several signals at 4.0–3.5 and 2.0–1.0 ppm, which corresponds to the terminal and inner protons of spacers, respectively. Their unambiguous assignment is performed with the help of combination of the ^{1}H–^{15}N/^{13}C HMBC correlations of the protons of the terminal methylene group and the heterocyclic fragments (Fig. 1). A number of NOEs strongly support these assignments (see Supplementary data (SD)).

A good agreement of the calculated (GIAO DFT)[27–30] versus experimental ^{13}C chemical shifts (R^2>0.99, SD) has additionally confirmed the structures and assignments of the terminal protons of the spacers of **A** and **B** isomers.

In fact, each spin system of the spacers can be unequivocally detailed by the 1D TOCSY method (Fig. 2). As soon as the protons of the terminal methylene groups of the spacers are established, the heterocyclic fragments can be easily combined into a single whole. As a result it is found that the isomer **A** has the *syn*-arrangement of the $C_{ur}{}^4$=O and C_{imid}–S bonds (Fig. 2a–c), while in the isomer **B** there occurs the *anti*-arrangement of those bonds (Fig. 2d–f). Thus, the first isomer from the eluted fractions has the structure of the heterocyclophane **13a**, and the structure of the heterocyclophane **13b** is assigned to the second isomer (Scheme 5).

The difference in mutual orientation of heterocyclic moieties of isomers **13a**,**b** causes their different UV/vis absorption(Fig. 3). On the Fig. 3 it is shown that UV/vis absorbance of the *anti*-isomer **13b** exceeds that of the *syn*-isomer **13a**.

Intramolecular interactions between uracil and benzimidazole moieties in heterocyclophanes in the $CHCl_3$ solution have been interpreted in terms of hypochromism, i.e., the decrease of light absorbance compared with monomeric compounds. The concentrations were low enough to preclude formation of intermolecular complexes. The last phenomenon, i.e., hypochromism has been widely used as an evidence of the stacked structures of various π-systems, including nucleic acid bases in solution.[8] This approach has recently been applied to pyrimidinophanes with three uracil fragments.[11,31]

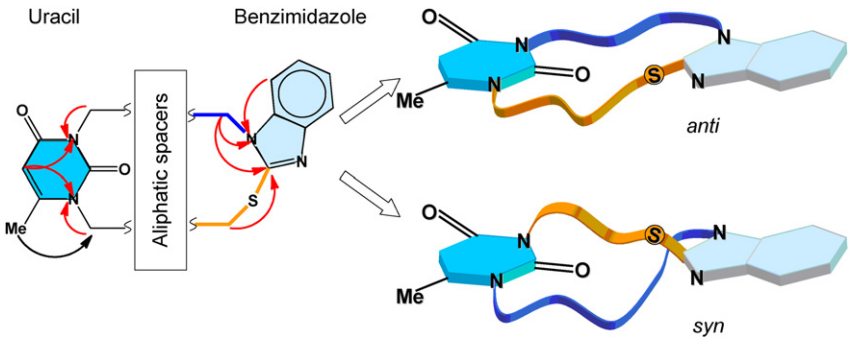


Fig. 1. The principal HMBC ^{1}H–^{15}N/^{13}C (red arrows mean correlations between protons and atoms of N and C) and NOEs key correlations (black arrows) for **A** isomer, possible *anti*- and *syn*-arrangement of $C_{ur}{}^4$=O and C_{imid}–S bonds.

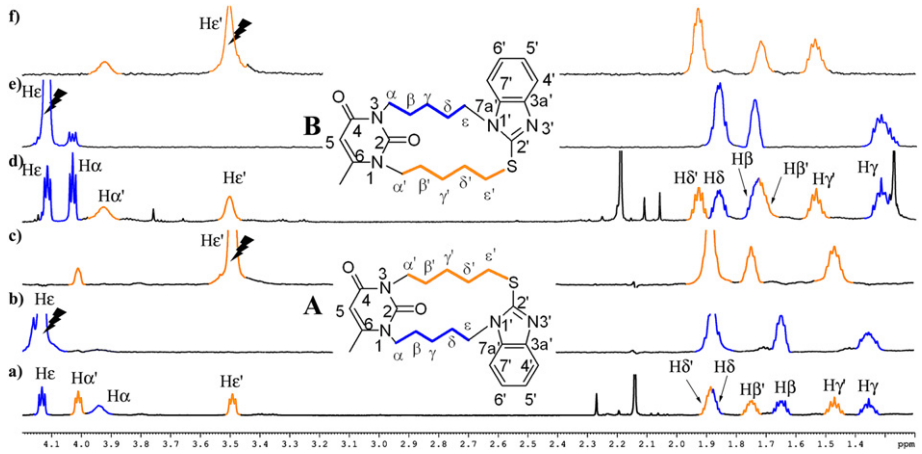


Fig. 2. Low field fragments of ^{1}H NMR and TOCSY NMR spectra of macrocyclic isomers **A** and **B** in $CDCl_3$ at 313 K (for isomer **A**) and 303 K (for isomer **B**): (a, d) ^{1}H NMR spectra; (b, C, e, f) 1D TOCSY NMR spectra (excited protons are marked by an arrow) of the isomers, individual spin-systems are marked out with color.

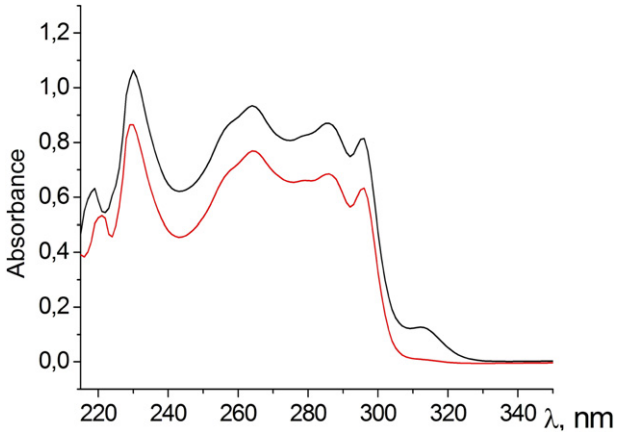


Fig. 3. UV/vis absorbance spectra of 0.5 mM $CHCl_3$ solutions of compounds **13a** (red line) and **13b** (black line).

Heterocyclophanes **13a**,**b** consist of 6-methyluracil and 2-thiobenzimidazole units, which are simulated by the reference compounds 1,3-bis(4-bromobutyl)-6-methyluracil (**15**)[11] and 1-pentyl-2-thiopentylbenzimidazole (**16**), respectively (Fig. 4). Values of hypochromism were calculated from the oscillator strength, $f=4.32\times10^{-9}\int(\varepsilon(\lambda)/\lambda^2)d\lambda$, of the heterocyclophanes **13a**,**b** and reference compounds **15** and **16**. In calculating the hypochromism, $\%H=\{1-[f_{\mathbf{13a,b}}/(f_{\mathbf{15}}+f_{\mathbf{16}})]\}100$, of the heterocyclophanes, f is the oscillator strength of macrocycle **13a** or **13b**, and $f_{\mathbf{15}}+f_{\mathbf{16}}$ is the sum of the oscillator strengths of reference compounds. The following f values were obtained: 0.206[31] and 0.308 for reference compounds **15** and **16**, respectively, 0.475 and 0.509 for macrocyclic isomers **13a**,**b**, respectively. Value of f for *anti*-isomer **13b** is almost additive to f values of the reference compounds **15** and **16**, as a result there is practically no hypohromism (H=1%). On the contrary, the *syn*-isomer **13a** exhibits a slight hypochromic effect with H=7.6%, and this indicates that in $CHCl_3$ solution of the macrocycle conformations with closed uracil and benzimidazole units are possible. This implies that the distance between the uracil and benzimidazole moieties in the macrocycle **13a** and their mutual orientation provide intramolecular π–π-interactions, which cause the hypochromic effect. Thus, it is assumed that the degree of interaction between the uracil and benzimidazole bases in isomeric heterocyclophane **13a** with *syn*-arrangement of the $C_{ur}{}^4$=O and C_{imid}–S bonds is higher than the interaction in isomeric heterocyclophane **13b** with the *anti*-arrangement of these bonds. This allows, but not dictates, a greater percentage of internally stacked versus unfolded conformations in the $CHCl_3$ solution of the *syn*-isomer **13a** than that in solution of the *anti*-isomer **13b**.

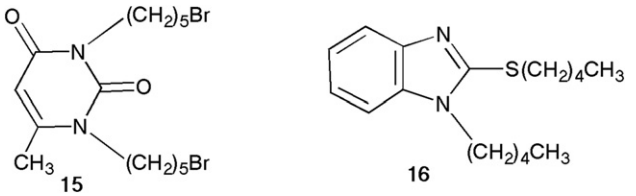


Fig. 4. Reference compounds for calculating the hypochromic effect of heterocyclophanes **13a**,**b**, which simulate the 6-methyluracil and 2-thiobenzimidazole units of the macrocycles.

2.3. Reactivity of 1,3-bis[5-(benzimidazole-2-ylthio-1*H*)pentyl]uracils

Substituted benzimidazoles are a widely used structural motif in drug discovery. In particular, 2-substituted benzimidazoles have been core structures of many biochemically important compounds.[32–34] From this point of view it is of interest to study the further chemical modifications of the 1,3-bis[5-(benzimidazole-2-ylthio-1*H*)pentyl]uracils obtained and especially of compounds **12a**,**c**. The compounds have been introduced in the reactions of alkylation of the imide functions, quaternization of the N atoms and oxidation of the S atoms of the benzimidazole moieties.

Compounds **12a**,**c** are smoothly alkylated with CH_3I under standard conditions (NaH, DMF, rt) affording bismethylated products **17a**,**b** with good isolated yields (Fig. 5). This approach has been employed for heterocyclophane preparation. Compound **12c** was subjected to ring-closure reaction at the imide groups with *meta*-bis(bromomethyl)benzene under the same conditions. The 17% yield of the cyclized product **18** (Fig. 5) seems to be acceptable for this type of the reactions.

The quaternizing of N atoms into the imidazole rings of the compounds **12a**,**c** was aimed at screening different kinds of biological activity, as the quaternization of N atoms can provide the solubility in polar solvents. The alkylation of benzimidazole N atoms of compounds **17a**,**b** with methyliodide or methyl ether of *para*-toluenesulfonic acid was carried out by hours-long heating of the compounds in CH_3CN. Compounds **19a**,**b** (Fig. 5) were isolated with almost quantitative yields. Some features of NMR ^{1}H spectra of the compounds **19a**,**b** are worth emphasizing. Signals of all CH_3-protons at N atoms of benzimidazole moieties resonate at the

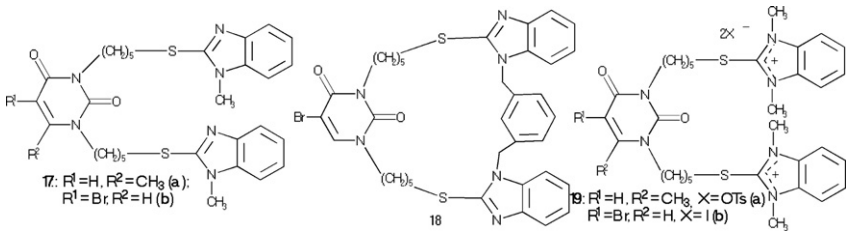


Fig. 5. Structures of the alkylation products of the compounds **12a**,**c**.

downfield region 4.20–4.30 ppm. Due to the symmetry of the substituted benzimidazole fragments in the compounds **19a**,**b** and therefore the delocalization of positive charge between both imidazole N atoms, it is impossible to assign unambiguously the quaternized N atom.

Substituted benzimidazoles at the 2-position with sulfinyl groups are an important class of biologically active compounds. Effective inhibitors of the acid-secreting gastric (H^+, K^+)-ATPase[35] and selective nonsteroidal progestin agonists[36] are among them. Oxidation to sulfinyl moiety has been carried out with *meta*-chloroperoxybenzoic acid.[36,37] This procedure was applied to 2-thiobenzimidazoles, which are bridged with uracil derivative, i.e., compound **12a**. Oxidation of thioalkyl substituents of the compound **12a** to sulfinyl groups with *m*-CPBA afforded disulfoxide **20** with 20% isolated yield (Fig. 6). Further oxidation of the compound **20** has been performed according to the established protocol in the presence of a buffer solution of $NaHCO_3$ using catalytic amounts of $MnSO_4 \cdot H_2O$ (1 mol %) and 30% H_2O_2.[38] Under these conditions an almost quantitative decomposition of the disulfoxide **20** occurred, and as a result the 'uracilic' part of the compound **20** gave diol **21**. We have not succeeded in isolating oxidation products of the '2-thiobenzimidazolic' part of the compound **20**. However, the MSEI analysis showed that the formation of the sulfinyl **22** and sulfonyl **23** acids (Fig. 6) took place in the oxidation process.

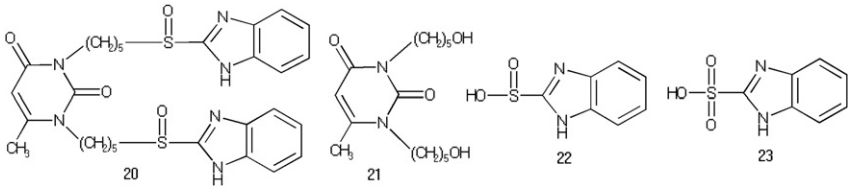


Fig. 6. Structures of the oxidation products of the compound **12a**.

In summary, the terminal atoms of Br in 1,3-bis(bromoalkyl)uracils are easily replaced by mercapto-substituted five-membered heterocycles, in particular thiadiazoles, imidazole, and benzimidazoles. If the mercapto-group is a single reaction site at the heterocycle bissubstituted products are isolated with satisfactory yields. This results in the case of reaction of 2-mercapto-5-methyl-1,3,4-thiadiazole with 1,3-bis(bromopentyl)-6-methyluracil. The occurrence of the second center at the heterocycle, especially the imide function or the mercapto-group significantly complicates the reactions of the heterocycle with bisbromopentyl derivatives of 6-methyluracil and 5-bromouracil. Reactions of the dibromides with 2,5-dimercapto-1,3,4-thiadiazole and 2-mercaptobenzimidazole afforded a series of acyclic and macrocyclic compounds. Heterocyclophanes with a nucleotide base derivative, in particular the uracil derivative bridged with other five-membered heterocycles have been prepared for the first time. These heterocyclophanes are of interest as geometric isomers with different mutual arrangement, trans or cis of $C_{ur}{}^4$=O-group at pyrimidine rings or regioisomers with a different bonding mode of the uracil derivative and the heterocyclic 2-thiobenzimidazolic fragment. Regioisomers demonstrate distinct UV/vis absorbance and a hypochromic effect with respect to model compounds. Mercapto- and imide functions in the heterocyclic moieties of the acyclic substituted uracils are subjected to the reactions of ring-closure, alkylation, and oxidation. This allows us to vary the structure of the compounds over a wide range.

3. Experimental section

3.1. General methods

NMR experiments were carried out with Bruker spectrometers AVANCE-400 (400.1 MHz (^{1}H), 100.6 MHz (^{13}C)) and AVANCE-600 (600.1 MHz (^{1}H), 150.9 MHz (^{13}C), 60.8 MHz (^{15}N)) equipped with a pulsed gradient unit capable of producing magnetic field pulse gradients in the *z*-direction of 53.5 G cm^{-1}. All spectra were acquired in a 5-mm gradient inverse broad band probehead. Chemical shifts are reported on the δ (ppm) scale and are relative to the residual ^{1}H and ^{13}C signal of DMSO-d_6 and $CDCl_3$. Chemical shifts of **13a**,**b** were determined within the DFT framework using a hybrid exchange-correlation functional, B3LYP, at the 6-31G(d) level as implemented in Gaussian 98.[39] Full geometry optimizations were performed at the ab initio RHF/6-31G level. All data were referred to TMS (^{1}H and ^{13}C) chemical shifts that were calculated in the same conditions.

MALDI-TOF mass spectra were obtained on a Bruker ULTRAFLEX mass spectrometer in *p*-nitroaniline matrix. The IR spectra of the compounds (KBr pellets or oil) were recorded on a Vector 22 FTIR Spectrometer (Bruker) in the 4000–400 cm^{-1} range at a resolution of 1 cm^{-1}. UV/vis absorbance measurements were made with Perkin–Elmer Lambda 25 UV/vis spectrometer. The uncorrected melting points were measured on the Boetius apparatus. Elemental analysis data were obtained on a CHN-3 analyzer. TLC was carried out on the Silufol-254 plates, development in the UV light.

Commercially available heterocycles 2-mercapto-5-methyl-1,3,4-thiadiazole (**2**) (Lancaster), 2,5-dimercapto-1,3,4-thiadiazole (**3**) (Lancaster), 2-mercaptoimidazole (**4**), 2-mercaptobenzoimidazole (**5a**) (Lancaster), and 2-mercapto-5-nitrobenzimidazole (**5b**) (Acros) were used without purification. 1,3-Bis(5-bromopentyl-1)-6-methyluracil (**1a**) and 1,3-bis(bromopentyl-1)-5-bromouracil (**1b**) have been prepared according to the known protocol.[10,21] Column chromatography was carried out on SiO_2 (0.06–0.2 mm) from Acros. All the solvents and reagents were dried before use.

3.2. General procedure for the introduction of heterocycles to *N*-alkyl derivatives of 6-methyluracil and 5-bromouracil

NaH (2 or 4 equiv) was added to a suspension of heterocycle (2 equiv) in DMF and the mixture was stirred at room temperature for 1 h. Dibromide (1 equiv) in DMF was dropped and contents were stirred at room temperature until the consumption of the dibromide on TLC plates (6–12 h). The solvent was removed in a vacuum and the residue was treated with $CHCl_3$, filtered, concentrated and subjected to column chromatography on SiO_2.

*3.2.1. 1,3-Bis[5-(5-methyl-1,3,4-thiadiazole-2-ylthio)pentyl]-6-methyluracil (**6**).* Compound **6** was prepared from heterocycle **2** (1.58 g, 12.0 mmol), NaH (0.29 g, 12.0 mmol), and dibromide **1a** (2.50 g, 6.0 mmol) in DMF (65 mL). The column was eluted in succession with petroleum ether and EtOAc/CH_3OH (30:1). Elution with the solvent mixture gave 2.21 g (70%) of compound **6** as an oily substance. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.56 (s, 1H, $C_{ur}{}^5H$), 3.91 (t, J=7.3 Hz, 2H, $N_{ur}{}^3CH_2$), 3.80 (t, J=7.3 Hz, 2H, $N_{ur}{}^1CH_2$), 3.36–3.26 (m, 4H, $2SCH_2$), 2.72 (s, 3H, $C_{tda}{}^5CH_3$), 2.71 (s, 3H, $C_{tda}{}^5CH_3$), 2.23 (s, 3H, $C_{ur}{}^6CH_3$), 1.86–1.81 (m, 4H, $2CH_2$), 1.69–1.64 (m, 4H, $2CH_2$), 1.54–1.49 (m, 4H, $2CH_2$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 165.4, 164.8, 31.8, 31.7, 31.5, 29.0, 28.8, 28.7, 28.6, 28.0, 26.8, 25.8, 25.7, 25.4, 23.8, 19.4 ppm; IR (ν/cm^{-1}, oil): 3001, 2934, 2859, 1699, 1659, 1622, 1466, 1431, 1403, 1382, 1189, 1062, 1044, 973, 817, 754, 664, 624, 547; MALDI-MS (m/z): calcd for $C_{21}H_{30}N_6O_2S_4$ $[M]^+$, $[M+Na]^+$ and $[M+K]^+$ 526.1, 549.1 and 565.1, found: 526.1, 549.1 and 565.1. Anal. Calcd for $C_{21}H_{30}N_6O_2S_4$: C, 47.88; H, 5.74; N, 15.95; S, 24.35. Found: C, 47.83; H, 5.72; N, 15.81; S, 24.23.

*3.2.2. 1,3-Bis[5-(5-mercapto-1,3,4-thiadiazole-2-ylthiopenthyl)-5-bromouracil (**7**) and isomeric heterocyclophanes **10**a,**b**.* Compounds **7** and **10a**,**b** were prepared from heterocycle **3** (1.53 g, 10.0 mmol), NaH (0.24 g, 10 mmol), and dibromide **1b** (2.50 g, 5.0 mmol) in DMF (80 mL). The column was eluted in succession with petroleum ether and $CHCl_3$/CH_3OH (80:1). Elution with the solvent mixture gave 0.14 g (3%) of isomeric heterocyclophanes **10a**,**b** mixture as an oily substance. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (br s, 2H, $2C_{ur}{}^6H$), 4.00 (m, 4H, $2N_{ur}{}^3CH_2$), 3.76 (m, 4H, $2N_{ur}{}^1CH_2$), 3.32–3.25 (m, 8H, $4SCH_2$), 1.88–1.82 (m, 8H, $4CH_2$), 1.77 (m, 4H, $2CH_2$), 1.68 (m, 4H, $2CH_2$), 1.55–1.47 (m, 8H, $4CH_2$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 164.9, 159.2, 150.6, 141.9, 128.3, 96.1, 49.9, 42.4, 34.0, 33.6, 28.7, 26.9, 25.9, 25.1 ppm; IR (ν/cm^{-1}, oil): 3053, 2929, 2856, 1706, 1655, 1446, 1382, 1277, 1210, 1038, 907, 759, 681, 606, 555; MALDI-MS (m/z): calcd for $C_{32}H_{42}Br^{79}{}_2N_8O_4S_6$ $[M+H]^+$, $[M+Na]^+$ 953.0, 975.0, found: 952.8, 974.8. Anal. Calcd for $C_{32}H_{42}Br_2N_8O_4S_6$: C, 40.25; H, 4.43; N, 11.73; S, 20.15; Br, 16.74. Found: C, 40.16; H, 4.36; N, 11.82; S, 20.26; Br, 16.81. The following elution with the solvent mixture gave 0.93 g (29%) of compound **7**, oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H, $C_{ur}{}^6H$), 3.99 (t, J=7.4 Hz, 2H, $N_{ur}{}^3CH_2$), 3.77 (t, J=7.2 Hz, 2H, $N_{ur}{}^1CH_2$), 3.30 (br s, 2H, 2SH), 3.15–3.10 (m, 4H, $2SCH_2$), 1.83–1.77 (m, 4H, $2CH_2$), 1.69–1.66 (m, 4H, $2CH_2$), 1.50–1.46 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.2, 150.7, 144.3, 94.5, 79.5, 49.2, 42.0, 33.6, 28.7, 28.6, 28.1, 26.7, 25.5, 25.0 ppm; IR (ν/cm^{-1}, oil): 3143, 2936, 2858, 2756, 1709, 1646, 1491, 1449, 1380, 1338, 1256, 1117, 1052, 907, 759, 712, 653, 610, 553; MALDI-MS (m/z): calcd for $C_{18}H_{23}Br^{79}N_6O_2S_6$ $[M]^+$ 625.9, found: 626.1. Anal. Calcd for $C_{18}H_{23}BrN_6O_2S_6$: C, 34.44; H, 3.69; N, 13.39; S, 30.65; Br, 12.73. Found: C, 34.30; H, 3.73; N, 13.32; S, 30.56; Br, 12.82.

*3.2.3. Heterocyclophane **9**.* A solution of iodine (0.29 g, 1.1 mmol) in $CHCl_3$ (100 mL) was added dropwise for 3 h to a solution of compound **7** (0.75 g, 1.2 mmol) and NEt_3 (0.12 g, 1.2 mmol) in the mixture of $CHCl_3$ (200 mL) and CH_3OH (50 mL) at room temperature, and the mixture was allowed to stand at the same temperature overnight. It was concentrated to 1:3 of the initial volume and washed in succession with 100 mL of water with a few crystals of sodium thiosulfate added, and water (2×100 mL), and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was subjected to column chromatography on silica gel in solution of EtOAc. The column was eluted with petroleum ether and EtOAc. Elution with EtOAc gave 0.35 g (47%) of heterocyclophane **9**. Yellow solid; mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H, $C_{ur}{}^6H$), 4.01 (t, J=7.5 Hz, 2H, $N_{ur}{}^3CH_2$), 3.75 (t, J=7.5 Hz, 2H, $N_{ur}{}^1CH_2$), 3.34–3.25 (m, 4H, $2SCH_2$), 1.88–1.82 (m, 4H, $2CH_2$), 1.69–1.65 (m, 4H, $2CH_2$), 1.51–1.47 (m, 4H, $2CH_2$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 164.3, 163.8, 159.2, 150.6, 141.8, 96.1, 49.9, 42.4, 34.2, 33.9, 29.7, 28.8, 28.6, 28.5, 26.8, 25.6, 25.1 ppm; IR (ν/cm^{-1}, KBr pellet): 2924, 2853, 1704, 1654, 1448, 1376, 1333, 1262, 1210, 1045, 758, 665, 607, 553; MALDI-MS (m/z): calcd for $C_{18}H_{21}Br^{79}N_6O_2S_6$ $[M+H]^+$, $[M+Na]^+$ 624.9, 646.9, found: 625.4, 647.4. Anal. Calcd for $C_{18}H_{21}BrN_6O_2S_6$: C, 34.55; H, 3.38; N, 13.43; S, 30.75; Br, 12.77. Found: C, 34.60; H, 3.33; N, 13.42; S, 30.69; Br, 12.72.

*3.2.4. 1,3-Bis[5-(imidazole-2-ylthio-1H)pentyl]-6-methyluracil (**11**).* Compound **11** was prepared from heterocycle **4** (0.88 g, 10.0 mmol), NaH (0.24 g, 10.0 mmol), and dibromide **1a** (2.12 g, 5.0 mmol) in DMF (60 mL). The column was eluted in succession with petroleum ether, $CHCl_3$/CH_3OH 40:1 and $CHCl_3$/CH_3OH 20:1. Elution with $CHCl_3$/CH_3OH 20:1 gave 1.24 g (58%) of compound **11** as an oily substance. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (br s, 2H, 2NH), 7.09 (br s, 4H, $2C_{imid}{}^4H$, $2C_{imid}{}^5H$), 5.58 (s, 1H, $C_{ur}{}^5H$), 3.92 (t, J=7.3 Hz, 2H, $N_{ur}{}^3CH_2$), 3.79 (t, J=7.3 Hz, 2H, $N_{ur}{}^1CH_2$), 2.97–2.93 (m, 4H, $2SCH_2$), 2.22 (s, 3H, $C_{ur}{}^6CH_3$), 1.70–1.60 (m, 8H, $4CH_2$), 1.44–1.36 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.7, 153.0, 151.9, 139.3, 124.1, 100.7, 44.8, 33.6, 33.5, 29.5, 29.4, 28.0, 27.1, 25.7, 25.5, 19.5 ppm; IR (ν/cm^{-1}, oil): 3108, 3011, 2929, 2858, 2761, 2679, 1698, 1656, 1619, 1531, 1465, 1431, 1408, 1361, 1327, 1267, 1211, 1095, 1047, 960, 817, 766, 688, 628, 581, 548; MALDI-MS (m/z): calcd for $C_{21}H_{30}N_6O_2S_2$ $[M+H]^+$, $[M+Na]^+$ 463.2, 485.2, found: 463.2, 485.2. Anal. Calcd for $C_{21}H_{30}N_6O_2S_2$: C, 54.52; H, 6.54; N, 18.17; S, 13.86. Found: C, 54.53; H, 6.49; N, 18.21; S, 13.80.

*3.2.5. 1,3-Bis[5-(benzimidazole-2-ylthio-1H)pentyl]-6-methyluracil (**12a**), isomeric heterocyclophanes **13a**,**b**, and oligomer **14**.* Compounds **12a**, **13a**, and **14** were prepared from heterocycle **5a** (3.56 g, 23.7 mmol), NaH (0.56 g, 23.7 mmol), and dibromide **1a** (5.00 g, 11.8 mmol) in DMF (150 mL). The column was eluted in succession with petroleum ether, EtOAc/CH_3OH 80:1, 50:1, 20:1, and 10:1 mixtures. Elution with the solvent mixture 80:1 gave 0.10 g (2%) of heterocyclophane **13a**. White solid; mp 170 °C; UV ($CHCl_3$) λ (log ε): 296 (4.14), 287 (4.16), 280 (4.14), 266 (4.19), 259 (4.17), 233 (4.14) nm; ^{1}H NMR ($CDCl_3$, 600 MHz) (Fig. 2): δ 7.66 (d, J=7.6 Hz, 1H, $H_{Ar}{}^{4'}$), 7.21 (d, J=7.6 Hz, 1H, $H_{Ar}{}^{7'}$), 7.20 (t, J=7.6 Hz, 1H, $H_{Ar}{}^{5'}$), 7.16 (t, J=7.6 Hz, 1H, $H_{Ar}{}^{6'}$), 5.47 (s, 1H, C^5H), 4.13 (t, J=5.8 Hz, 2H, $C^{\varepsilon}H_2$), 4.03 (t, J=5.6 Hz, 2H, $C^{\alpha'}H_2$), 3.94 (m, 2H, $C^{\alpha}H_2$), 3.49 (t, J=6.0 Hz, 2H, $C^{\varepsilon'}H_2$), 2.14 (s, 3H, C^6CH_3), 1.91–1.89 (m, 2H, $C^{\delta'}H_2$), 1.88–1.86 (m, 2H, $C^{\delta}H_2$), 1.75 (dt, J=6.2 and 5.7 Hz, 2H, $C^{\beta'}H_2$), 1.65 (dt, J=6.2 Hz, 2H, $C^{\beta}H_2$), 1.47 (qt, J=7.6 Hz, 2H, $C^{\gamma'}H_2$), 1.37–1.36 (m, 2H, $C^{\gamma}H_2$) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 162.2 (C^4), 152.8 (C^2), 152.6 ($C^{2'}$), 150.9 (C^6), 143.7 ($C^{3a'}$), 135.8 ($C^{7a'}$), 121.6 ($C^{5'}$), 121.4 ($C^{6'}$), 118.2 ($C^{4'}$), 118.2 ($C^{4'}$), 108.5 ($C^{7'}$), 43.8 (C^{ε}), 43.8 (C^{α}), 40.5 ($C^{\alpha'}$), 32.0 ($C^{\varepsilon'}$), 29.9 (C^{β}), 29.54 (C^{δ}), 27.5 ($C^{\delta'}$), 27.3 ($C^{\beta'}$), 24.5 ($C^{\gamma'}$), 23.7 (C^{γ}), 19.5 (CH_3) ppm; ^{15}N NMR ($CDCl_3$, 61 MHz): δ 163.8 (N^3), 149.0 ($N^{1'}$), 138.3 (N^1) ppm; IR (ν/cm^{-1}, KBr pellet): 3049, 2929, 2851, 1702, 1659, 1472, 1428, 1395, 1383, 1351, 1285, 1243, 1210, 1172, 1152, 1090, 1049, 1011, 923, 810, 768, 737, 628, 554; MALDI-MS (m/z): calcd for $C_{22}H_{28}N_4O_2S$ $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ 413.2, 435.2,

451.2, found: 413.1, 435.2, 451.2. Anal. Calcd for $C_{22}H_{28}N_4O_2S$: C, 64.05; H, 6.84; N, 13.58; S, 7.77. Found: C, 64.09; H, 6.86; N, 13.61; S, 7.72. Subsequent fractions of the solvent mixture gave 0.10 g (2%) of isomeric heterocyclophane **13b**. White solid; mp 190 °C; UV ($CHCl_3$) λ (log ε): 313 (3.36), 296 (4.19), 286 (4.21), 280 (4.19), 265 (4.25), 258 (4.21), 234 (4.20) nm; ^{1}H NMR ($CDCl_3$, 400 MHz) (Fig. 2): δ 7.65 (d, J=7.5 Hz, 1H, $H_{Ar}{}^{4'}$), 7.26–7.18 (m, 3H, $H_{Ar}{}^{5'}$, $H_{Ar}{}^{6'}$, $H_{Ar}{}^{7'}$), 5.41 (s, 1H, C^5H), 4.11 (t, J=5.6 Hz, 2H, $C^{\varepsilon}H_2$), 4.03 (t, J=5.9 Hz, 2H, $C^{\alpha'}H_2$), 3.95–3.91 (m, 2H, $C^{\alpha}H_2$), 3.52–3.48 (m, 2H, $C^{\varepsilon'}H_2$), 2.19 (s, 3H, C^6CH_3), 1.93 (dt, J=6.2 and 6.4 Hz, 2H, $C^{\delta'}H_2$), 1.87–1.85 (m, 2H, $C^{\delta}H_2$), 1.75–1.73 (m, 2H, $C^{\beta}H_2$), 1.73–1.71 (m, 2H, $C^{\beta'}H_2$), 1.54 (dt, J=7.4 and 8.4 Hz, 2H, $C^{\gamma'}H_2$), 1.33–1.31 (m, 2H, $C^{\gamma}H_2$) ppm; ^{13}C NMR ($CDCl_3$): δ 162.3 (C^4), 152.8 (C^2), 152.3 ($C^{2'}$), 151.2 (C^6), 143.4 ($C^{3a'}$), 135.8 ($C^{7a'}$), 121.7 ($C^{5'}$, $C^{6'}$), 117.8 ($C^{4'}$), 108.9 ($C^{7'}$), 101.9 (C^5), 44.3 (C^{ε}), 44.1 ($C^{\alpha'}$), 40.9 (C^{α}), 31.8 ($C^{\varepsilon'}$), 29.5 (C^{δ}), 29.1 ($C^{\beta'}$), 27.6 (C^{β}), 27.5 ($C^{\delta'}$), 24.7 ($C^{\gamma'}$), 24.0 (C^{γ}), 19.0 (CH_3) ppm; ^{15}N NMR ($CDCl_3$, 61 MHz): δ 162.6 (N^3), 150.1 ($N^{1'}$), 139.5 (N^1) ppm; IR (ν/cm^{-1}, KBr pellet): 3051, 2925, 2851, 1698, 1663, 1467, 1424, 1397, 1381, 1345, 1299, 1272, 1243, 1197, 1155, 1129, 1095, 1078, 1050, 1008, 884, 815, 766, 700, 627, 556; MALDI-MS (m/z): calcd for $C_{22}H_{28}N_4O_2S$ $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ 413.2, 435.2, 451.2, found: 413.1, 435.2, 451.2. Anal. Calcd for $C_{22}H_{28}N_4SO_2$: C, 64.05; H, 6.84; N, 13.58; S, 7.77. Found: C, 64.02; H, 6.88; N, 13.59; S, 7.74. The following elution with EtOAc/CH_3OH 20:1 mixture afforded 3.23 g (49%) of compound **12a**. White solid; mp 110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (br s, 2H, 2NH), 7.50–7.48 (m, 4H, $4H_{Ar}$), 7.18–7.15 (m, 4H, $4H_{Ar}$), 5.54 (s, 1H, $C_{ur}{}^5H$), 3.94 (t, J=7.0 Hz, 2H, $N_{ur}{}^3CH_2$), 3.94 (t, J=7.3 Hz, 2H, $N_{ur}{}^1CH_2$), 3.27 (t, J=7.3 Hz, 2H, CH_2S), 3.21 (t, J=7.3 Hz, 2H, CH_2S), 2.14 (s, 3H, $C_{ur}{}^6CH_3$), 1.77–1.79 (m, 4H, $2CH_2$), 1.62–1.66 (m, 4H, $2CH_2$), 1.41–1.43 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.8, 152.9, 151.9, 150.6, 144.1, 135.8, 121.9, 121.5, 117.7, 110.7, 100.8, 95.9, 44.8, 31.5, 31.4, 29.4, 28.1, 27.1, 25.8, 25.6, 19.5 ppm; IR (ν/cm^{-1}, KBr pellet): 3139, 3057, 2935, 2860, 2808, 1698, 1655, 1618, 1496, 1469, 1432, 1402, 1359, 1293, 1268, 1226, 1147, 1117, 1048, 979, 816, 745, 665, 629, 582, 550, 435; MALDI-MS (m/z): calcd for $C_{29}H_{34}N_6O_2S_2$ $[M]^+$, $[M+Na]^+$ 562.2, 585.2, found: 562.2, 585.2. Anal. Calcd for $C_{29}H_{34}N_6O_2S_2$: C, 61.89; H, 6.09; N, 14.93; S, 11.40. Found: C, 61.86; H, 6.06; N, 14.82; S, 11.35. The following elution with EtOAc/CH_3OH 10:1 mixture gave 0.35 g (3%) of oligomer **14**. Oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (br s, 2H, 2NH), 7.51–7.47 (m, 4H, $4H_{Ar}$), 7.18–7.14 (m, 8H, $8H_{Ar}$), 5.55 (s, 1H, $C_{ur}{}^5H$), 5.53 (s, 1H, $C_{ur}{}^5H$), 4.12–4.08 (m, 2H, $N_{benzim}CH_2$), 3.95–3.91 (m, 4H, $2N_{ur}{}^3CH_2$), 3.79–3.73 (m, 4H, $2N_{ur}{}^1CH_2$), 3.38–3.22 (m, 6H, $3CH_2S$), 2.18 (s, 3H, $C_{ur}{}^6CH_3$), 2.17 (s, 3H, $C_{ur}{}^6CH_3$), 1.85–1.79 (m, 8H, $4CH_2$), 1.69–1.63 (m, 8H, $4CH_2$), 1.47–1.43 (m, 8H, $4CH_2$) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 161.8, 151.6, 151.4, 151.2, 150.4, 150.3, 143.1, 139.3, 135.8, 121.4, 117.6, 113.7, 110.0, 108.7, 101.2, 95.8, 44.6, 43.6, 40.6, 32.1, 25.9, 25.1 ppm; IR (ν/cm^{-1}, oil): 3189, 3107, 2934, 2864, 1696, 1654, 1618, 1463, 1431, 1407, 1362, 1325, 1302, 1267, 1109, 1048, 1008, 974, 817, 746, 663, 624, 547, 421; MALDI-MS (m/z): calcd for $C_{51}H_{62}N_{10}O_4S_3$ $[M+H]^+$, $[M+Na]^+$ 975.4, 997.4, found: 975.7, 997.7. Anal. Calcd for $C_{51}H_{62}N_{10}O_4S_3$: C, 62.81; H, 6.41; N, 14.36; S, 9.86. Found: C, 62.82; H, 6.35; N, 14.41; S, 9.78.

*3.2.6. 1,3-Bis[5-(5-nitrobenzimidazole-2-ylthio-1H)pentyl]-6-methyluracil (**12b**).* Compound **12b** was prepared from heterocycle **5b** (2.24 g, 11.6 mmol), NaH (0.28 g, 11.6 mmol), and dibromide **1a** (2.46 g, 5.8 mmol) in DMF (100 mL). The column was eluted in succession with petroleum ether and EtOAc/CH_3OH 80:1. Elution with the solvent mixture gave 2.0 g (53%) of compound **12b**. Yellow solid; mp 130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.26 (s, 1H, NH), 10.91 (s, 1H, NH), 8.52 (br s, 2H, $2H_{Ar}$), 8.27–8.30 (m, 2H, $2H_{Ar}$), 8.12–8.14 (m, 2H, $2H_{Ar}$), 5.65 (s, 1H, $C_{ur}{}^5H$), 3.99 (t, J=7.3 Hz, 2H, $N_{ur}{}^3CH_2$), 3.89 (t, J=7.3 Hz, 2H, $N_{ur}{}^1CH_2$), 3.33 (t, J=7.2 Hz, 2H, SCH_2), 3.23 (t, J=7.2 Hz, 2H, SCH_2), 2.28 (s, 3H, $C_{ur}{}^6CH_3$), 1.90–1.87 (m, 8H, $4CH_2$), 1.74–1.72 (m, 4H, $2CH_2$), 1.51–1.49 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.9, 161.8, 156.9, 153.0, 151.9, 142.5, 117.8, 100.7, 95.9, 44.7, 36.3, 31.4, 31.3, 31.2, 29.2, 28.0, 27.0, 25.8, 25.6, 19.4 ppm; IR (ν/cm^{-1}, oil): 3173, 3097, 3020, 2940, 2862, 1697, 1650, 1619, 1514, 1469, 1428, 1360, 1332, 1277, 1263, 1226, 1065, 969, 944, 820, 790, 735, 664, 626, 548, 461, 438; MALDI-MS (m/z): calcd for $C_{29}H_{32}N_8O_6S_2$ $[M+2H]^+$, $[M+H+Na]^+$ 654.2, 676.2, found: 653.9, 675.9. Anal. Calcd for $C_{29}H_{32}N_8O_6S_2$: C, 53.36; H, 4.94; N, 17.17; S, 9.82. Found: C, 53.33; H, 4.99; N, 17.20; S, 9.80.

*3.2.7. 1,3-Bis[5-(benzimidazole-2-ylthio-1H)pentyl]-5-bromouracil (**12c**).* Compound **12c** was prepared from heterocycle **5a** (1.82 g, 12.1 mmol), NaH (0.29 g, 12.1 mmol), and dibromide **1b** (3.0 g, 6.1 mmol) in DMF (80 mL). The column was eluted in succession with petroleum ether, EtOAc/CH_3OH 50:1 and 40:1 mixtures. Elution with the solvent mixture 40:1 gave 1.25 g (33%) of compound **12c**. White solid; mp 120 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.30 (s, 1H, NH), 8.28 (s, 1H, NH), 7.44–7.41 (m, 5H, $4H_{Ar}$, $C_{ur}{}^6H$), 7.12–7.08 (m, 4H, $4H_{Ar}$), 3.83 (t, 2H, J=7.3 Hz, $N_{ur}{}^3CH_2$), 3.73 (t, 2H, J=7.3 Hz, N^1CH_2), 3.29–3.24 (m, 4H, $2CH_2S$), 1.75–1.73 (m, 4H, $2CH_2$), 1.64–1.62 (m, 2H, CH_2), 1.55–1.53 (m, 2H, CH_2), 1.44–1.39 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.2, 150.6, 144.3, 144.2, 121.8, 95.9, 94.4, 49.3, 42.1, 31.5, 31.4, 29.3, 29.2, 28.2, 26.9, 25.2 ppm; IR (ν/cm^{-1}, KBr pellet): 3145, 3050, 3004, 2938, 2860, 2781, 2693, 2604, 1707, 1655, 1502, 1441, 1423, 1396, 1352, 1270, 1231, 1209, 1154, 1073, 1049, 1010, 983, 902, 845, 752, 666, 629, 604, 557, 438; MALDI-MS (m/z): calcd for $C_{28}H_{31}Br^{79}N_6O_2S_2$ $[M+H]^+$, $[M+Na]^+$ 627.1, 649.1, found: 627.1, 649.1. Anal. Calcd for $C_{28}H_{31}BrN_6O_2S_2$: C, 53.58; H, 4.98; N, 13.39; S, 10.22; Br, 12.73. Found: C, 53.59; H, 4.86; N, 13.31; S, 10.12; Br, 12.69.

*3.2.8. 1-Pentyl-2-thiopentylbenzimidazole (**16**).* Compound **16** was obtained by the same procedure. In particular, the mixture of NaH (0.49 g, 20.0 mmol) and heterocycle **5a** (1.50 g, 10.0 mmol) was stirred in DMF (60 mL) at room temperature for 2 h. 1-Bromopentane (3.10 g, 21.0 mmol) was added and the stirring was continued at 65–70 °C for 5 h. Volatiles were removed in a vacuum, the residue was treated with $CHCl_3$, filtered, concentrated and subjected to column chromatography on SiO_2. The column was eluted in succession with petroleum ether and petroleum ether/ether 3:1. Elution with the solvent mixture gave 2.25 g (78%) of compound **16** as an oily substance. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68–7.66 (m, 1H, H_{Ar}) 7.25–7.17 (m, 3H, $3H_{Ar}$), 4.06 (t, 2H, J=7.3 Hz, $N_{benzim}CH_2$), 3.41–3.37 (t, 2H, J=7.3 Hz, CH_2S), 1.81–1.77 (m, 4H, $2CH_2$), 1.46–1.34 (m, 8H, $4CH_2$), 0.91–0.89 (m, 6H, $2CH_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 143.7, 136.1, 121.5, 118.2, 108.6, 44.1, 32.6, 30.9, 29.0, 29.0, 28.9, 22.3, 22.2, 13.9, 13.8 ppm; IR (ν/cm^{-1}, oil): 3057, 3036, 2957, 2930, 2860, 1460, 1434, 1378, 1358, 1269, 1243, 1190, 1132, 1009, 925, 820, 739, 650, 610, 554, 432. Anal. Calcd for $C_{17}H_{26}N_2S$: C, 70.29; H, 9.02; N, 9.64; S, 11.04. Found: C, 70.35; H, 8.96; N, 9.60; S, 10.90.

3.3. General procedure for the alkylation of benzoimidazole moieties of compound 12a,c

NaH (2 equiv) was added to a solution of compound **12a**,**c** (1 equiv) in DMF and the mixture was stirred at room temperature for 2 h. Solution of methyliodide (2 equiv) or *meta*-bis(-bromomethyl)benzene (1 equiv) in DMF was added and the reaction mixture was stirred at room temperature for 10 h. The solvent was removed in a vacuum and the residue was treated with

$CHCl_3$, filtered, concentrated and subjected to column chromatography on SiO_2.

*3.3.1. 1,3-Bis[5-(1-methylbenzimidazole-2-ylthio)pentyl]-6-methyluracil (**17a**).* Compound **17a** was prepared from compound **12a** (2.0 g, 3.6 mmol), NaH (0.15 g, 6.2 mmol), and CH_3I (0.90 g, 6.3 mmol) in DMF (60 mL). The column was eluted in succession with petroleum ether, $CHCl_3/CH_3OH$ 20:1 mixture. Elution with the solvent mixture gave 1.74 g (82%) of compound **17a**. Oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.63 (m, 2H, $2H_{Ar}$), 7.23–7.19 (m, 6H, $6H_{Ar}$), 5.52 (s, 1H, $C_{ur}{}^5H$), 3.91 (t, 2H, J=7.3 Hz, $N_{ur}{}^3CH_2$), 3.79 (2H, J=7.6 Hz, $2N_{ur}{}^1CH_2$), 3.67 (s, 6H, $2N_{benzim}CH_3$), 3.40–3.35 (m, 4H, $2CH_2S$), 2.20 (s, 3H, $C_{ur}{}^6CH_3$), 1.87–1.83 (m, 4H, $2CH_2$), 1.71–1.67 (m, 4H, $2CH_2$), 1.55–1.51 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.6, 152.7, 151.4, 150.2, 143.7, 135.2, 121.0, 120.7, 117.1, 110.2, 100.3, 95.4, 44.0, 34.2, 34.0, 31.1, 30.8, 28.8, 27.6, 26.6, 25.3, 25.0, 19.4 ppm; IR (ν/cm^{-1}, oil): 3051, 2935, 2860, 1695, 1654, 1618, 1503, 1469, 1432, 1402, 1360, 1220, 1185, 1127, 1038, 1005, 817, 749, 667, 628, 578, 552, 435; MALDI-MS (m/z): calcd for $C_{31}H_{38}N_6O_2S_2$ $[M+H]^+$, $[M+Na]^+$ 591.3, 613.3, found: 591.3, 613.3. Anal. Calcd for $C_{31}H_{38}N_6O_2S_2$: C, 63.02; H, 6.48; N, 14.22; S, 10.86. Found: C, 62.94; H, 6.45; N, 14.23; S, 10.76.

*3.3.2. 1,3-Bis[5-(1-methylbenzimidazole-2-ylthio)pentyl]-5-bromouracil (**17b**).* Compound **17b** was prepared from compound **12c** (0.75 g, 1.2 mmol), NaH (0.06 g, 2.5 mmol), and CH_3I (0.38 g, 2.7 mmol) in DMF (50 mL). The column was eluted in succession with petroleum ether, $CHCl_3/CH_3OH$ 40:1 mixture. Elution with the solvent mixture gave 1.74 g (76%) of compound **17b**. Oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66–7.63 (m, 2H, $2H_{Ar}$), 7.51 (s, 1H, $C_{ur}{}^6H$), 7.23–7.19 (m, 6H, $6H_{Ar}$), 3.98 (t, 2H, J=7.5 Hz, $N_{ur}{}^3CH_2$), 3.75 (2H, J=7.2 Hz, $2N_{ur}{}^1CH_2$), 3.67 (s, 6H, $2N_{benzim}CH_3$), 3.40–3.36 (m, 4H, $2CH_2S$), 1.88–1.68 (m, 8H, $4CH_2$), 1.55–1.51 (m, 4H, $2CH_2$) ppm; MALDI-MS (m/z): calcd for $C_{30}H_{35}BrN_6O_2S_2$ $[M+H]^+$ 655.1, found: 655.2; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.0, 150.2, 143.9, 143.5, 121.1, 95.2, 93.9, 49.0, 34.7, 34.5, 31.1, 30.8, 28.8, 28.5, 28.4, 26.4, 24.7 ppm; IR (ν/cm^{-1}, oil): 3030, 2935, 2858, 1703, 1657, 1502, 1470, 1446, 1396, 1340, 1270, 1241, 1208, 1154, 1130, 1049, 1011, 922, 810, 753, 666, 610, 555. Anal. Calcd for $C_{30}H_{35}N_6O_2S_2Br$: C, 54.95; H, 5.38; N, 12.82; S, 9.78; Br, 12.19. Found: C, 55.04; H, 5.36; N, 12.86; S, 9.76; Br, 12.25.

*3.3.3. Heterocyclophane (**18**).* Compound **18** was obtained from compound **12c** (1.94 g, 3.1 mmol), NaH (0.15 g, 6.2 mmol), and *meta*-bis(bromomethyl)benzene (0.90 g, 3.4 mmol) in DMF (60 mL). The column was eluted in succession with petroleum ether and EtOAc. Elution with EtOAc gave 0.39 g (17%) of macrocycle **18**. White solid; mp 73 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68–7.66 (m, 2H, $2H_{Ar}$), 7.52–7.48 (m, 2H, $2H_{Ar}$), 7.38 (s, 1H, $C_{ur}{}^6H$), 7.25–7.11 (m, 8H, $8H_{Ar}$), 5.24 (s, 2H, $N_{benzim}CH_2$), 5.21 (s, 2H, $N_{benzim}CH_2$), 4.00–3.96 (m, 2H, $N_{ur}{}^3CH_2$), 3.74–3.69 (m, 2H, $N_{ur}{}^1CH_2$), 3.41–3.31 (m, 4H, $2CH_2S$), 1.74–1.64 (m, 10H, $5CH_2$), 1.50–1.48 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 150.6, 141.9, 135.7, 129.5, 126.4, 122.5, 118.2, 118.1, 109.2, 109.1, 96.1, 60.3, 49.8, 47.4, 42.4, 42.1, 33.1, 32.8, 31.9, 29.7, 28.4, 26.9, 25.2 ppm; IR (ν/cm^{-1}, KBr pellet): 3056, 2927, 2856, 1704, 1656, 1446, 1413, 1337, 1280, 1243, 1047, 990, 908, 744, 559, 424; MALDI-MS (m/z): calcd for $C_{36}H_{37}Br^{79}N_6O_2S_2$ $[M+H]^+$ 729.2, found: 729.4. Anal. Calcd for $C_{36}H_{37}BrN_6O_2S_2$: C, 59.25; H, 5.11; N, 11.52; S, 8.79; Br, 10.95. Found: C, 59.24; H, 5.14; N, 11.54; S, 8.72; Br, 10.83.

3.4. General procedure for the quaternization of N atoms of benzoimidazole moieties of compound 17a,b

A solution of compound **17a**,**b** (1 equiv) and methyliodide or methyl ether of *para*-toluenesulfonic acid (5 equiv) in CH_3CN (30 mL) was refluxed for 30 h. The solvent was distilled off. The residue was thoroughly triturated in ethyl ether (3×20 mL), each time decantated and finally the solvent was evaporated.

*3.4.1. 1,3-Bis[5-(1,3-dimethylbenzimidazolinium-2-ylythio)-pentyl]-6-methyluracil ditosylate (**19a**).* Compound **19a** was obtained from compound **17a** (0.46 g, 0.8 mmol) and methyl tosylate (0.74 g, 4.0 mmol) in CH_3CN (40 mL). Yield 0.76 g (100%); oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76–7.70 (m, 4H, $4H_{Ar}$), 7.58–7.52 (m, 4H, $4H_{Ar}$), 7.45 (d, 4H, J=7.8 Hz, $4H_{Ar}$), 6.99 (d, 4H, J=7.4 Hz, $4H_{Ar}$), 5.48 (s, 1H, $C_{ur}{}^5H$), 4.20 (s, 6H, $2N_{benzim}CH_3$), 4.19 (s, 6H, $2N_{benzim}CH_3$), 3.88–3.84 (m, 2H, $N_{ur}{}^3CH_2$), 3.77–3.71 (m, 2H, $N_{ur}{}^1CH_2$), 3.40–3.36 (m, 2H, CH_2S), 3.29–3.25 (m, 2H, CH_2S), 2.28 (br s, 9H, $C_{ur}{}^6CH_3$, $2CH_3Ph$), 1.85–1.46 (m, 12H, $6CH_2$); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 162.1, 151.8, 148.1, 148.0, 144.4, 138.9, 132.3, 128.3, 127.4, 127.3, 125.7, 113.0, 101.1, 95.8, 44.5, 36.1, 36.0, 33.6, 29.4, 29.2, 27.8,26.4, 25.1, 21.0, 19.5 ppm; IR (ν/cm^{-1}, oil): 3065, 3036, 2934, 2862, 1694, 1654, 1618, 1505, 1467, 1432, 1402, 1360, 1219, 1183, 1121, 1033, 1009, 819, 756, 682, 567. Anal. Calcd for $C_{47}H_{58}N_6O_8S_4$: C, 58.60; H, 6.07; N, 8.72; S, 13.32. Found: C, 58.50; H, 6.00; N, 8.69; S, 13.24.

*3.4.2. 1,3-Bis[5-(1,3-dimethylbenzimidazolinium-2-ylthio)-pentyl]-5-bromouracil diiodide (**19b**).* Compound **19b** was obtained from compound **17b** (0.50 g, 0.8 mmol) and methyliodide (0.60 g, 4.2 mmol) in CH_3CN (40 mL). Yield 0.76 g (90%); brown oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79–7.75 (m, 2H, $2H_{Ar}$), 7.71–7.67 (m, 2H, $2H_{Ar}$), 7.50 (s, 1H, $C_{ur}{}^6H$), 7.19–7.15 (m, 4H, $4H_{Ar}$), 4.30 (s, 6H, $2N_{benzim}CH_3$), 4.29 (s, 6H, $2N_{benzim}CH_3$), 4.01–3.97 (m, 2H, $N_{ur}{}^3CH_2$), 3.80–3.76 (m, 2H, $N_{ur}{}^1CH_2$), 3.21–3.17 (m, 4H, $2CH_2S$), 1.88–1.42 (m, 12H, $6CH_2$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.2, 150.7, 149.1, 144.2, 132.7, 127.5, 113.9, 95.8, 94.5, 49.1, 35.9, 33.9, 33.8, 29.8, 29.7, 28.1, 26.7, 25.5, 25.0 ppm; IR (ν/cm^{-1}, oil): 3019, 2930, 2856, 1701, 1652, 1503, 1478, 1449, 1397, 1339, 1280, 1260, 1211, 1134, 1014, 823, 803, 758, 663, 611, 561, 422. Anal. Calcd for $C_{32}H_{41}BrI_2N_6O_2S_2$: C, 40.91; H, 4.40; N, 8.94; S, 6.83; Br, 8.50; I, 27.01. Found: C, 41.96; H, 4.36; N, 8.91; S, 6.86; Br, 8.45; I, 27.10.

3.5. Oxidation of 2-thiobenzoimidazole derivative 12a

*3.5.1. 1,3-Bis[5-(benzimidazole-2-ylsulfinyl-1H)pentyl]-6-methyluracil (**20**).* To a solution of compound **12a** (0.60 g, 1.1 mmol) in 30 mL of $CHCl_3$ at −3 °C was added *m*-CPBA (0.50 g, 3.2 mmol in 15 mL of $CHCl_3$, 70% purity). The reaction mixture was stirred at room temperature for 30 min and then washed with 40 mL of $NaHCO_3$ (5.00 g, 60.0 mmol) aqueous solution. The $CHCl_3$ layer was separated, concentrated and subjected to column chromatography on SiO_2. The column was eluted in succession with petroleum ether, $EtOAc/CH_3OH$ 30:1 and 20:1 mixtures. Elution with the solvent mixture 20:1 gave 1.13 g (20%) of compound **20**. White solid; mp 75–76 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79–7.77 (m, 2H, $2H_{Ar}$), 7.63–7.61 (m, 2H, $2H_{Ar}$), 7.35–7.32 (m, 4H, $4H_{Ar}$), 5.44 (s, 1H, $C_{ur}{}^5H$), 3.83 (t, 2H, J=7.0 Hz, $N_{ur}{}^3CH_2$), 3.72 (t, 2H, J=7.0 Hz, $N_{ur}{}^1CH_2$), 3.35–3.31 (m, 4H, $2CH_2S$), 2.08 (s, 3H, $C_{ur}{}^6CH_3$), 1.85–1.83 (m, 4H, $2CH_2$), 1.66–1.63 (m, 4H, $2CH_2$), 1.45–1.42 (m, 4H, $2CH_2$) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.8, 154.4, 153.0, 151.9, 123.7, 100.7, 53.6, 53.5, 44.6, 28.1, 27.1, 25.7, 25.4, 21.521.4, 19.4 ppm; IR (ν/cm^{-1}, KBr pellet): 3141, 3040, 2939, 2864, 1698, 1654, 1469, 1434, 1404,1359, 1297, 1268, 1220, 1036, 964, 801, 767, 747, 628, 548; MALDI-MS (m/z): calcd for $C_{29}H_{34}N_6O_4S_2$ $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ 595.2, 617.2, 633.2, found: 595.3, 617.3, 633.3. Anal. Calcd for $C_{29}H_{34}N_6O_4S_2$: C, 58.56; H, 5.76; N, 14.13; S, 10.78. Found: C, 58.61; H, 5.80; N, 14.12; S, 10.75.

*3.5.2. 1,3-Bis(5-hydroxypentyl)-6-methyluracil (**21**).* To a stirred solution of compound **12a** (1.00 g, 1.8 mmol) and $MnSO_4$ monohydrate (3.0 mg, 1 mol %) in DMF (60 mL) an aqueous mixture comprised by 30% H_2O_2 (1 mL, 10.0 mmol) and a 0.2 M buffer

solution of $NaHCO_3$ (20 mL) was added. The reaction mixture was stirred for 15 min at room temperature and filtered. The solvent was distilled off and the residue was treated with $CHCl_3$. The formed precipitate was filtered and analyzed by MS (EI). The $CHCl_3$ filtrate was concentrated and subjected to column chromatography on SiO_2. The column was eluted in succession with petroleum ether, CH_2Cl_2, and CH_2Cl_2/CH_3OH 10:1 mixture. Elution with the solvent mixture afforded 0.44 g (82%) of compound **21**. Oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.57 (s, 1H, $C_{ur}{}^5H$), 3.94 (t, 2H, J=7.2 Hz, $N_{ur}{}^3CH_2$), 3.81 (t, 2H, J=7.6 Hz, $N_{ur}{}^1CH_2$), 3.67–3.62 (m, 4H, $2CH_2O$), 2.24 (s, 3H, $C_{ur}{}^6CH_3$), 1.71–1.65 (m, 6H, $2CH_2$, 2OH), 1.65–1.61 (m, 4H, $2CH_2$), 1.47–1.42 (m, 4H, $2CH_2$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 152.1, 151.2, 101.7, 62.4, 62.2, 45.0, 41.1, 32.2, 32.0, 28.7, 27.2, 23.0, 19.7 ppm; IR (ν/cm^{-1}, oil): 3434, 2938, 2864, 1695, 1656, 1616, 1469, 1432, 1323, 1210, 1074, 1056, 961, 919, 819, 770, 732, 629, 553, 451. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.41; H, 8.81; N, 9.42.

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Supplementary data

NOE spectra and calculated chemical shifts of regioisomeric heterocyclophanes. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.07.034.

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