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Synthesis of New Sulfur-Containing Derivatives of Furanoallocolchicinoids

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Abstract—Reaction of hydroxyl-containing heterocyclic colchicinoids with S-nucleophiles led to the formation of furanoallocolchicinoid sulfides in a high yield.

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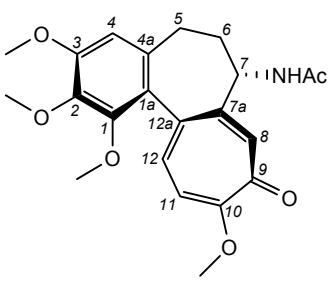
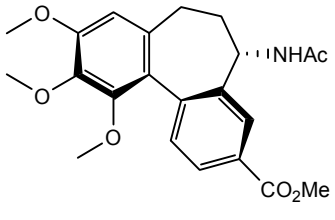
Colchicine **1**, an alkaloid isolated from *Colchicum autumnale*, is the first known inhibitor of polymerization of tubulin – the protein underlying the microtubules of the mitotic spindle during cell division [1]. On the molecular level colchicine prevents the self-assembly of tubulin interacting with it on the boundary between its α- and β-forms. This domain is named "colchicine site of tubulin" [2]. These interactions result in inhibition of mitosis (nonsexual cell division) and in decreased cell mobility [3]. In the clinical practice colchicine is used in the treatment of Mediterranian fever, Behcet disease, gout, chondrocalcinosis, and other types of arthritis [4–7]. Indications are mentioned for the treatment of liver cirrhosis, psoriasis, amyloidosis, diverse dermatitis, necrotizing vasculitis, Sweet's syndrome [8–11]. Colchicine may be potentially applied for the treatment of cardiovascular disorders [12], in particular, in the therapy of pericarditis, atrial fibrillation caused by inflammation, ischemia [13].

Colchicine exhibits as well the antitumor action [14], but its large doses possess considerable inherent toxicity, mainly due to the neurotoxicity and to the accumulation in the digestive tract [15]. Although the colchicines itself cannot be used for the treatment of cancer, its structural analogs (allocolchicine **2** [16], Z-stilbenes [17, 18], 4-arylcoumarins [19–22]) represent interesting objects in the search for new anticancer agents.

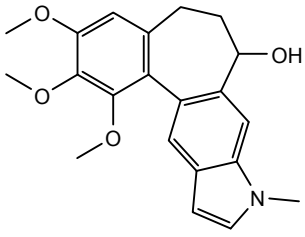
Introducing of pyrrole and furan fragments to the skeleton of the allocolchicinoid by coupling the seven-membered and six-membered rings **B** and **C** lead to compounds **3** and **4** with the improved antitumor and antitubulin activities [23–25]. Furanoallocolchicines **4** efficiently inhibit *in vivo* the growth of tumors without



(–)-(a*R*,7*S*)-Colchicine **1**



(–)-Allocolchicine **2**



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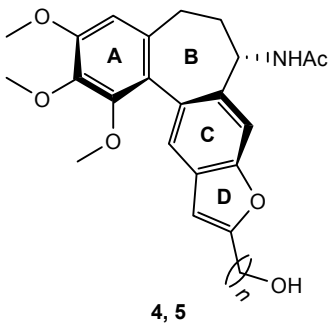
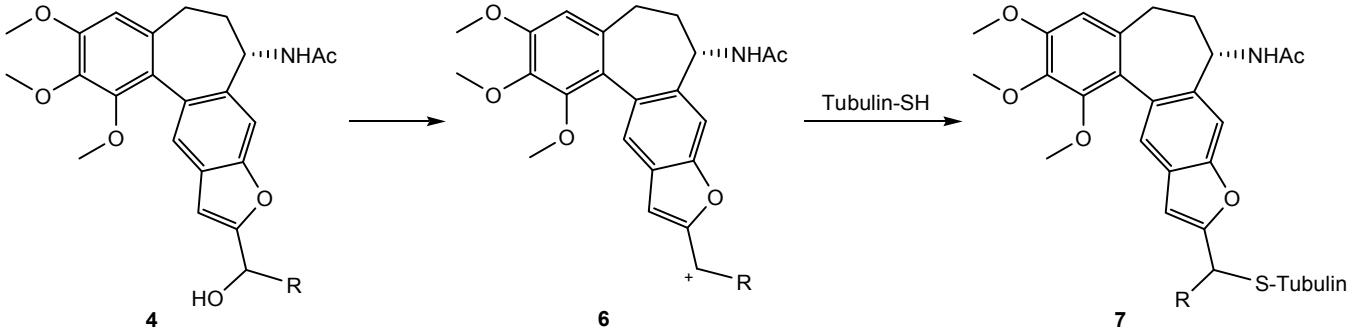


4, 5

n = 1 (**4**), 2 (**5**).

Scheme 1.

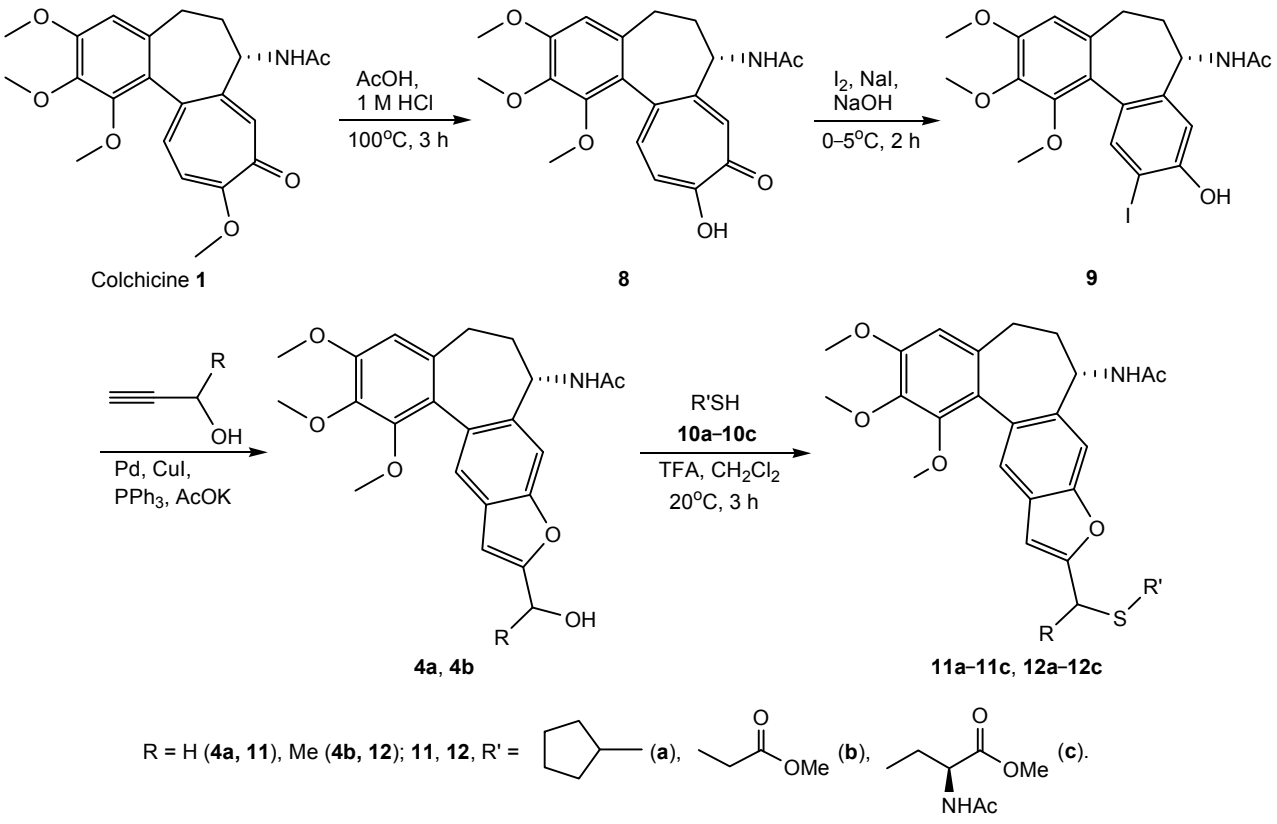


the neurologic symptoms, weight loss, and mortality of experimental animals [24]. The presence of hydroxyl groups in the benzyl position of ring **B** (compound **3**) or in the pseudobenzyl position of ring **D** (compound **4**) considerably increases the antitumor activity. At the same time the transition of the hydroxy group from the pseudobenzyl hydroxymethyl position (colchicinoid **4**) to the hydroxyethyl one (colchicinoid **5**) results in a drastic loss of the antitumor activity. The heterocyclic allocolchicinoids are a new class of organic derivatives unknown prior to our investigations [26].

To explain the high of allocolchicinoids **3** and **4** to suppress the cell growth (antiproliferation activity) we have proposed a hypothesis that these compounds are capable to form the benzylic and pseudobenzylic cations **6** stable under the physiological conditions (Scheme 1) with further covalent binding to the free cysteine fragment of the cellular protein tubulin.

In this connection we examined the model reactions of the derivatives **4a** and **4b** with S-nucleophiles: cyclopentyl mercaptan, protected thioglycolic acid,

Scheme 2.



and protected cysteine (Scheme 2). Furanoallocolchicines **4a** and **4b** were prepared from natural colchicine in three steps. In the first stage colchicine **1** was converted in colchiceine **8** by treating with 1 M HCl [27]. Therein the tropolone ether function of colchicine **1** is removed. After extraction the yield of compound **8** was 98%.

In the second stage colchiceine **8** was transformed into iodocolchinol **9** according to the Windaus procedure [27, 28]. In these conditions the seven-membered ring undergoes an electrophilic oxidative contraction by alkali and iodination in the presence of a mixture of iodine and sodium iodide [27].

Synthesized furanoallocolchicines **4a** and **4b** interacted effectively with S-nucleophiles **10a–10c** in acid medium [29] which results in target sulfides **11a–11c** and **12a–12c** in 73–97% yields.

The antiproliferative activity of allocolchicinoids **11** and **12** was investigated against cell cultures MiaPaCa-2, A549, and HEK293. Unlike the initial derivatives **4a** and **4b** exhibiting the cytotoxic activity in nanomolar concentrations [24], allocolchicinoid sulfides **11** and **12** possess practically no antiproliferative activity.

Thus sulfides of furanoallocolchicinoids were synthesized by reactions of hydroxyl-containing colchicinoids with sulfanyl derivatives in high yields. The performed transformations confirm our hypothesis on the possibility of covalent bonding with the cell protein tubulin of heterocyclic allocolchicinoids containing hydroxyl fragments in benzylic and pseudobenzylic positions. The hydroxy group in the benzylic position is a fundamentally important pharmacophore of the colchicine derivatives.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker AV 600, Bruker DRX 500, Bruker AV 400, Bruker ARX 400, Agilent DD2 400, or Bruker DPX 300. Chemical shifts were measured from the residual protons of the deuterated solvent $(CD_3)_2SO$ (δ 2.50 ppm). ^{13}C NMR spectra were obtained on spectrometers Bruker AV 600 (150 MHz), Bruker DRX 500 (126 MHz), Bruker AV 400 (100 MHz), Bruker ARX 400 (101 MHz), or Agilent DD2 400 (101 MHz). Chemical shifts were reported from $(CD_3)_2SO$ (δ 39.52 ppm). Mass spectra were measured on an instrument DSQ with a quadrupole mass analyzer. Temperature of the ion source 230°C, EI, 70 eV. High resolution mass spectra were taken on an instrument Finnigan MAT 900, EI, 70 eV. For column chromatography Alfa Aesar Silicagel 60 (70–230 mesh) was used. Commercially available reagents (Aldrich, Alfa Aesar, Acros) were used without additional purification. Solvents were purified by standard procedures. Petroleum ether was of bp 40–65°C.

***N*-{(7*S*)-10-(Hydroxymethyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta[1',2':4,5]-benzo[1,2-*b*]furan-7-yl}acetamide (4a).** To a mixture of 200.0 mg (0.414 mmol) of compound **9**, 4.7 mg (0.021 mmol) of $Pd(OAc)_2$, 8.0 mg (0.041 mmol) of CuI, 16.3 mg (0.062 mmol) of PPh_3, and 121.7 mg (1.242 mmol) of AcOK under an argon atmosphere 4 mL of anhydrous acetonitrile was added. Then 24.8 μL (0.414 mmol) of propargyl alcohol was added dropwise. The obtained solution was stirred for 1 h at 60°C and 12 h at 80°C (TLC monitoring). After cooling to room temperature the reaction product was isolated by column chromatography on silica gel, eluent petroleum ether–ethyl acetate–ethanol, 5 : 1 : 1. Yield 143.1 mg (84%), light-brown crystals, mp 110°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.85–2.16 m (4H, CH_2CH_2), 1.90 s (3H, CH_3CO), 3.42 s (3H, 2-MeO), 3.79 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 4.56 s (2H, CH_2OH), 4.64–4.68 m (1H, CHNH), 6.75 s ($1H_{arom}$), 6.79 s (1H, CH), 7.46 s ($1H_{arom}$), 7.51 s ($1H_{arom}$), 8.47 d (1H, NH, *J* 8.5 Hz). ^{13}C NMR spectrum (101 MHz), δ, ppm: 22.67, 30.05, 38.37, 48.40, 54.91, 56.22, 60.45, 60.59, 103.21, 105.52, 108.01, 121.81, 124.73, 126.18, 128.69, 134.75, 137.42, 140.59, 150.37, 152.23, 153.73, 158.42, 168.39. Mass spectrum, *m/z* (I_{rel}, %): 411 (55), 353 (23), 352 (100), 337 (43), 321 (57), 294 (17). $C_{23}H_{25}NO_6$. Calculated *M* 411.45.

***N*-{(7*S*)-10-(1-Hydroxyethyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta[1',2':4,5]-benzo[1,2-*b*]furan-7-yl}acetamide (4b)** was obtained similarly. Yield 163.9 mg (93%), light-brown crystals, mp 80°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.47 d (3H, C<u>H</u>$_3$CH, *J* 6.4 Hz), 1.85 d.d (1H, CH_2CH_2, *J* 12.2, 6.6 Hz), 1.89 s (3H, CH_3CO), 2.05 d.d (1H, CH_2CH_2, *J* 12.5, 6.9 Hz), 2.16 d.d (2H, CH_2CH_2, *J* 12.1, 6.1 Hz), 3.41 s (3H, 2-MeO), 3.79 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 4.63–4.55 m (1H, C<u>H</u>NH), 5.49 d (1H, OH, *J* 5.1 Hz), 6.70 s ($1H_{arom}$), 6.79 s (1H, CH), 7.45 s ($1H_{arom}$), 7.50 s ($1H_{arom}$), 8.45 d (1H, NH, *J* 8.3 Hz). ^{13}C NMR spectrum (101 MHz), δ, ppm:

18.56, 22.03, 22.68, 48.43, 55.83, 56.03, 60.46, 60.60, 62.33, 101.22, 105.55, 108.03, 121.79, 124.79, 126.17, 128.65, 134.77, 137.24, 140.61, 150.39, 152.24, 153.48, 162.01, 168.43. Mass spectrum, *m*/*z* (I_{rel}, %): 425 (62), 367 (26), 366 (100), 351 (42), 335 (42), 321 (24). $C_{24}H_{27}NO_6$. Calculated *M* 425.48.

***N*-{(7*S*)-10-Hydroxy-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl}acetamide (8).** A solution of 1.50 g (3.75 mmol) of colchicine **1** in 15 mL of acetic acid was mixed with 90 mL of 1 M HCl, the reaction mixture was stirred for 3 h at 100°C. On cooling to room temperature solid Na_2CO_3 was added till no odor of acetic acid remained (pH 6). The obtained yellow solution was extracted with chloroform (3 × 150 mL), the combined extracts were washed with brine, dried with Na_2SO_4, and evaporated in a vacuum. Yield 1.42 g (98%), greenish amorphous powder, mp 150°C [23]. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.87 s [3H, $CH_3C(O)$], 2.35–1.89 m (4H, CH_2CH_2), 3.56 s (3H, 2-MeO), 3.78 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 4.43–4.27 m (1H, CHNH), 6.80 s (1H, H^{11}), 7.15 d (1H, H^{12}, *J* 11.8 Hz), 7.31 s (1H, H^8), 7.32 s (1H, H^4), 8.63 d (1H, NH, *J* 7.3 Hz).

***N*-{(5*S*)-3-Hydroxy-2-iodo-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-yl}acetamide (9).** To a solution of 1.42 g (3.63 mmol) of compound **8** in 29 mL of water at 0°C was added in succession 1.45 g (36.30 mmol) of NaOH, dropwise 2.82 g (11.10 mmol) of iodine solution and 15.83 g (85.10 mmol) of NaI in 143 mL of water in the course of 1 h, then the mixture was stirred for 2 h at 0–5°C. Then the yellow-brown solution was warmed to room temperature, and equivalent amount of Na_2SO_3 was added to neutralize the excess of iodine. After that conc. HCl was added to pH 2, the precipitated yellow-green crystals were filtered off, washed with water, and dried in a vacuum. The mother liquor was extracted with ethyl acetate (3 × 150 mL), the combined extracts were washed with brine and dried with Na_2SO_4. On evaporating the solution the obtained yellowish crystals were added to those previously filtered off, and the product was chromatographed on a column packed with silica gel, eluent petroleum ether–ethyl acetate–ethanol, 8 : 1 : 1. Overall yield 1.25 g (70%), mp 238°C [23]. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.87 s [3H, $CH_3C(O)$], 2.23–1.87 m (4H, CH_2CH_2), 3.48 s (3H, 2-MeO), 3.77 s (3H, 3-MeO), 3.82 s (3H, 1-MeO), 4.33–4.40 m (1H, CHNH), 6.76 s ($1H_{arom}$), 6.86 s ($1H_{arom}$), 7.56 s ($1H_{arom}$), 8.38 d (1H, NH, *J* 8.0 Hz), 10.28 s (1H, OH).

Compounds 11a–11c and 12a–12c. General procedure. To a solution of compound **4a** and **4b** and the mercaptan in dichloromethane in an argon atmosphere was added dropwise trifluoroacetic acid (TFA), and the reaction mixture was stirred for 3 h at room temperature. On the completion of the reaction (TLC monitoring) the solvent was evaporated at a reduced pressure. Pure compounds **11a**–**11c** and **12a**–**12c** were isolated by column chromatography on silica gel.

***N*-{(7*S*)-1,2,3-Trimethoxy-10-[(cyclopentylsulfanyl)methyl]-6,7-dihydro-5*H*-benzo[6',7']cyclohepta[1',2':4,5]benzo[1,2-*b*]furan-1-yl}acetamide (11a)** was obtained from 30.0 mg (0.073 mmol) of compound **4a**, 28.1 μL (0.263 mmol) of cyclopentyl mercaptan, 0.3 mL of (3.9 mmol) TFA. Eluent for column chromatography dichloromethane–methanol, 100 : 1. Yield 30.1 mg (83%), white crystals, mp 118°C. ^{1}H NMR spectrum (500 MHz), δ, ppm: 1.41–1.59 m (5H, Cy), 1.64–1.70 m (2H, Cy), 1.83–1.89 m (1H, Cy), 1.91 s (3H, CH_3CO), 1.96–2.01 m (2H, CH_2CH_2), 2.05 d.d (1H, CH_2CH_2, *J* 12.8, 7.1 Hz), 2.13–2.20 m (1H, C_5H_9), 3.15 q (1H, CH_2CH_2, *J* 6.8 Hz), 3.43 s (3H, 1-MeO), 3.79 s (3H, 2-MeO), 3.84 s (3H, 3-MeO), 3.93 s (2H, CH_2SCy), 4.63–4.56 m (1H, CHNH), 6.76 s (1H, CH), 6.78 s ($1H_{arom}$), 7.45 s ($1H_{arom}$), 7.48 s ($1H_{arom}$), 8.42 d (1H, NH, *J* 8.5 Hz). ^{13}C NMR spectrum (126 MHz), δ, ppm: 22.64, 24.31, 24.32, 27.89, 32.98, 33.00, 43.20, 43.22, 48.39, 55.81, 60.44, 60.46, 60.53, 103.84, 105.41, 108.02, 121.56, 124.66, 126.27, 128.79, 134.71, 137.40, 140.57, 150.33, 152.22, 153.73, 155.33, 168.37. Found 496.2155 $[M + H]^+$. $C_{28}H_{34}NO_5S$. Calculated *M* 496.2152.

Methyl [({(7*S*)-7-(acetylamino)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta[1',2':4,5]-benzo[1,2-b]furan-10-yl}methyl)sulfanyl]acetate (11b) was obtained from 70.0 mg (0.170 mmol) of compound **4a**, 54.8 μL (0.612 mmol) of methyl thioacetate, 0.7 mL (9.1 mmol) of TFA. Eluent petroleum ether–ethyl-acetate–ethanol, 6 : 1 : 1. Yield 69.0 mg (81%), white crystals, mp 125°C. ^{1}H NMR spectrum (300 MHz), δ, ppm: 1.85 d.d (1H, CH_2CH_2, *J* 9.6, 4.0 Hz), 1.90 s (3H, CH_3CO), 1.95–2.27 m (3H, CH_2CH_2), 3.42 s (5H, CH_3OCOCH_2), 3.59 s (3H, 2-MeO), 3.79 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 4.02 s (2H, CH_2S), 4.59 d.t (1H, CHNH, *J* 11.8, 7.8 Hz), 6.77 s (1H, CH), 6.79 s ($1H_{arom}$), 7.45 s ($1H_{arom}$), 7.49 s ($1H_{arom}$), 8.46 d (1H, NH, *J* 8.4 Hz). ^{13}C NMR spectrum (126 MHz), δ, ppm: 22.63, 28.31, 29.99,

32.66, 38.30, 48.40, 51.99, 55.81, 60.45, 60.54, 104.74, 105.45, 108.03, 121.68, 124.63, 126.11, 128.87, 134.71, 137.69, 140.59, 150.34, 152.25, 153.86, 153.89, 168.38, 170.18. Found 522.1558 [*M* + Na]$^+$. $C_{26}H_{29}NO_7SNa$. Calculated *M* 522.1557.

Methyl *N*-acetyl-*S*-({(7*S*)-7-(acetylamino)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta-[1',2':4,5]benzo[1,2-*b*]furan-10-yl}methyl)-L-cysteinate (11c) was obtained from 75.0 mg (0.182 mmol) of compound **4a**, 116.3 mg (0.656 mmol) of *N*-acetyl-L-cysteine methyl ester, 0.75 mL (9.8 mmol) of TFA. Eluent petroleum ether–ethyl acetate–ethanol, 5 : 1 : 1. Yield 101.0 mg (97%), white crystals, mp 191°C. ^{1}H NMR spectrum (300 MHz), δ, ppm: 1.87 s [3H, $CH_3C(O)$], 1.90 s (3H, $SCH_2NH\underline{Ac}$), 1.96–2.31 m (3H, CH_2CH_2), 2.68–2.99 m (3H, CH_2CH_2, SCH_2NHAc), 3.43 s (3H, CH_3OCO), 3.64 s (3H, 2-MeO), 3.79 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 3.96 s (2H, CH_2S), 4.50–4.61 m (2H, 2CHNH), 6.77 s (1H, CH), 6.79 s ($1H_{arom}$), 7.45 s ($1H_{arom}$), 7.49 s ($1H_{arom}$), 8.45 t (2H, 2NH, *J* 7.8 Hz). ^{13}C NMR spectrum (126 MHz), δ, ppm: 22.24, 22.63, 27.97, 29.99, 32.47, 38.30, 48.40, 51.73, 52.02, 55.81, 60.46, 60.53, 104.42, 105.43, 108.02, 121.66, 124.63, 126.15, 128.86, 134.70, 137.60, 140.58, 150.33, 152.23, 153.82, 154.45, 168.36, 169.36, 171.14. Found 593.1931 [*M* + Na]$^+$. $C_{29}H_{34}N_2O_8SNa$. Calculated *M* 593.1928.

***N*-{(7*S*)-1,2,3-Trimethoxy-10-[1-(cyclopentylsulfanyl)ethyl]-6,7-dihydro-5*H*-benzo[6',7']-cyclohepta[1',2':4,5]benzo[1,2-*b*]furan-1-yl}acetamide (12a)** was obtained from 30.0 mg (0.071 mmol) of com-pound **4b**, 27.1 μL (0.254 mmol) of cyclopentyl mer-captan, 0.3 mL (3.9 mmol) TFA. Eluent dichloromethane–methanol, 100 : 1. Yield 26.4 mg (73%), white crystals, mp 155°C, diastereomers mixture. ^{1}H NMR spectrum (500 MHz), δ, ppm: 1.30–1.39 m (2H, SC_5H_9), 1.47–1.55 m (3H, SC_5H_9), 1.61 d.d (3H, $CHC\underline{H}_3$, *J* 7.1, 2.8 Hz), 1.66 d.d (2H, SC_5H_9, *J* 9.4, 4.9 Hz), 1.85–1.89 m (1H, SC_5H_9), 1.91 s [3H, $CH_3C(O)$], 1.97–2.21 m (4H, CH_2CH_2), 3.09 d.d (1H, SC_5H_9, *J* 14.6, 7.4 Hz), 3.43 d (3H, CH_3OC^1, *J* 8.6 Hz), 3.80 s (3H, CH_3OC^2), 3.84 s (3H, CH_3OC^3), 4.25 q (1H, $C\underline{H}CH_3$, *J* 7.0 Hz), 4.63–4.56 m (1H, C<u>H</u>NH), 6.75 s (1H, CH), 6.79 s ($1H_{arom}$), 7.46 d ($1H_{arom}$, *J* 6.0 Hz), 7.48 s ($1H_{arom}$), 8.41 d.d (1H, NH, *J* 8.5, 3.5 Hz). ^{13}C NMR spectrum (500 MHz), δ, ppm: 19.71, 19.81, 22.64, 22.66, 24.27, 24.28, 24.39, 30.00, 33.06, 33.10, 33.78, 36.62, 36.65, 38.34, 42.82, 42.94, 48.38, 48.40, 55.81, 60.44, 60.48, 60.52, 60.54, 102.28, 102.36, 105.47, 108.02, 121.63, 124.65, 124.68, 126.07, 128.76, 128.77, 134.70, 137.40, 137.43, 140.57, 150.32, 152.22, 153.45, 153.47, 159.16, 159.28, 168.37. Found 510.2311 [*M* + H]$^+$. $C_{29}H_{36}NO_5S$. Calculated *M* 510.2309.

Methyl [(1-{(7*S*)-7-(acetylamino)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta[1',2':4,5]-benzo[1,2-b]furan-10-yl}ethyl)sulfanyl]acetate (12b) was obtained from 70.0 mg (0.165 mmol) of compound **4b**, 53.0 μL (0.592 mmol) of methyl thioacetate, 0.7 mL (9.1 mmol) of TFA. Eluent petroleum ether–ethyl acetate–ethanol, 6 : 1 : 1. Yield 68.6 mg (81%), white crystals, mp 140°C, diastereomers mixture. ^{1}H NMR spectrum (600 MHz), δ, ppm: 1.63 d.d (3H, $CHC\underline{H}_3$ *J* 7.1, 2.4 Hz), 1.84–1.90 m (1H, CH_2CH_2), 1.91 s (3H, CH_3CO), 2.01–2.07 m (1H, CH_2CH_2), 2.12–2.21 m (1H, CH_2CH_2), 2.51–2.53 m (1H, CH_2CH_2), 3.35–3.42 m (2H, SCH_2), 3.43 d (3H, CH, *J* 5.4 Hz), 3.53 d (3H, 1-MeO, *J* 4.3 Hz), 3.80 s (3H, 3-MeO), 3.84 s (3H, 2-MeO), 4.36 q (1H, $C\underline{H}CH_3$, *J* 7.0 Hz), 4.59 d.d (1H, C<u>H</u>NH, *J* 19.3, 7.6 Hz), 6.76 s (1H, CH), 6.79 s ($1H_{arom}$), 7.46 d ($1H_{arom}$ *J* 6.1 Hz), 7.49 s ($1H_{arom}$), 8.42 d.d (1H, NH, *J* 8.3, 5.6 Hz). ^{13}C NMR spectrum (151 MHz), δ, ppm: 18.73, 22.64, 29.99, 32.28, 32.36, 48.43, 51.97, 55.81, 60.45, 60.54, 103.32, 105.51, 108.03, 121.74, 124.64, 125.88, 128.84, 134.70, 137.71, 140.59, 150.32, 152.24, 153.59, 157.59, 168.37, 170.26. Found 522.1558 [*M* + Na]$^+$. $C_{27}H_{31}NO_7SNa$. Calculated *M* 522.1557.

Methyl *N*-acetyl-*S*-(1-{(7*S*)-7-(acetylamino)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6',7']cyclohepta-[1',2':4,5]benzo[1,2-*b*]furan-10-yl}ethyl)-L-cysteinate (12c) was obtained from 80.0 mg (0.188 mmol) of compound **4b**, 119.9 mg (0.677 mmol) of N-acetyl-L-cysteine methyl ester, 0.8 mL (10.5 mmol) of TFA. Eluent petroleum ether–ethyl acetate–ethanol, 5 : 1 : 1. Yield 97.0 mg (88%), white crystals, mp 160°C, diastereomers mixture. ^{1}H NMR spectrum (300 MHz), δ, ppm: 1.60 d.d (3H, $CHC\underline{H}_3$, *J* 7.0, 3.8 Hz), 1.85 d (3H, SCHN<u>Ac</u>, *J* 4.7 Hz), 1.90 s [3H, $CH_3C(O)$], 1.92–2.33 m (3H, CH_2CH_2), 2.70–2.93 m (3H, CH_2S, CH_2CH_2), 3.43 d (3H, CH_3OCO, *J* 3.1 Hz), 3.61 d (3H, 2-MeO, *J* 3.8 Hz), 3.79 s (3H, 3-MeO), 3.84 s (3H, 1-MeO), 4.25–4.35 m (1H, $C\underline{H}CH_3$), 4.51–4.66 m (2H, 2C<u>H</u>NH), 6.76 d (1H, CH, *J* 3.6 Hz), 6.79 s ($1H_{arom}$), 7.45 d ($1H_{arom}$, *J* 2.0 Hz), 7.50 d ($1H_{arom}$, *J* 1.2 Hz), 8.39–8.48 m (2H, NH). ^{13}C NMR spectrum (126 MHz), δ, ppm: 18.50, 18.59, 21.65, 21.66, 22.08, 22.10, 25.85, 25.87, 29.68, 31.67, 31.85, 48.70, 52.23, 52.36, 52.39, 52.69, 56.33, 61.12, 61.14, 61.20, 104.92, 104.99, 107.62, 110.21, 124.34, 127.33, 127.35,

128.68, 131.69, 137.73, 140.76, 143.80, 153.85, 155.82, 157.18, 161.98, 162.07, 172.46, 173.39, 173.47, 175.23, 175.29. Found $[M + Na]^+$ 607.2090. $C_{30}H_{36}N_2O_8SNa$. Calculated *M* 607.2085.

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