Synthesis and studies of acetylthioglycoside conjugates of 4-chloro-1,2-dithiole-3-thione as potential antitumor agents

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Nucleophilic substitution of a chlorine atom in 4,5 dichloro-1,2-dithiole-3-thione with per-*O*-acetyl-1-mercaptho derivatives of D-glucose, D-galactose, D-mannose, D-xylose, L-arabinose, and D-maltose gave six new acetylthioglycoside conjugates of 4-chloro-1,2-dithiole-3-thione. These thioglycosides were shown to possess cancer preventive activity on the models of JB6 Cl41 P^+ mouse epidermal cells and THP-1 human leukemia cells in soft agar, as well as to inhibit the AP-1-dependent transcriptional activity in JB6 Cl41 luc-AP-1 cells, which suggests the possibility of using the new compounds as potential cancer preventive drugs.

Key words: sulfur-containing heterocycles, 4,5-dichloro-1,2-dithiole-3-thione, nucleophilic substitution, acetylthioglycosides, cancer preventive effect, inhibition of nuclear factor AP-1.

1,2-Dithiole-3-thiones (DTTs) are derivatives of five-membered pseudoaromatic heterocycles with various biological activities and interesting reactivity.[1—3] Although the first representatives of this class were synthesized at the beginning of the 20th century, their intensive study began after the report in 1985 by the pharmaceutical company "Rhone-Poulenc" about the use of 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione (Oltipraz) for the treatment of schistosomiasis, a common helminthic invasion in tropical regions of Africa and Latin America.[4] An in-depth study of Oltipraz showed that this drug has a wide range of biological properties, including cancer-preventive activity.[5—7] 1,2-Dithiole-3-thione derivatives were isolated from *Brassica oleracea*.[8] Six natural compounds of marine origin with a 1,2-dithiol fragment were isolated from ascidians, mangroves, and marine microbes.[9—12] To date, a large number of DTTs have been synthesized and their antiproliferative and cancer preventive activities have been investigated.[13] It was shown that DTTs exert a cancer preventive and cytoprotective effect by activating the Nrf2-ARE pathway and potent induction of phase II enzymes such as quinone reductase (QR) and glutathione *S*-transferase (GST).[14,15] Recently, it was found[16] that DTT efficiently inhibit the nuclear transcription factor NF-κB.

4,5-Dichloro-1,2-dithiole-3-thione (**1**) can serve as an attractive precursor for various heterocyclic systems (1,3-dithiols, imino-1,3-dithiethanes, 2-iminothiophen-3-ones, thienothiopyranthiones and many others) and functional derivatives of DTT due to its high reactivity in 1,3-dipolar addition and nucleophilic substitution reactions.[17—20] In this work, it is shown that new hybrid 5-acetylthioglycoside derivatives of 4-chloro-1,2-dithiole-3-thione, which are easily obtained by nucleophilic substitution of an active chlorine atom in 4,5-dichloro-1,2-dithiole-3-thione, exhibit a high anticancer activity and inhibit the pro-carcinogenic nuclear transcription factor AP-1.

Earlier, an efficient method for the preparation of 4,5-dichloro-1,2-dithiole-3-thione (**1**) has been developed[17] at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences and then it was established for the first time that the nucleophilic substitution occurs exclusively at position 5 of the heterocycle. Compound **1** was used as a basis for the synthesis of various aromatic *O*-, *N*- and *S*-derivatives, which were studied at the US National Cancer Institute (Bethesda) and showed to exhibit high anticancer activity *in vitro* against various types of human tumors.[21] At the same time, the studies carried out at the G. B. Elyakov Pacific Institute of Bioorganic Chemistry of the Far-Eastern Branch of the

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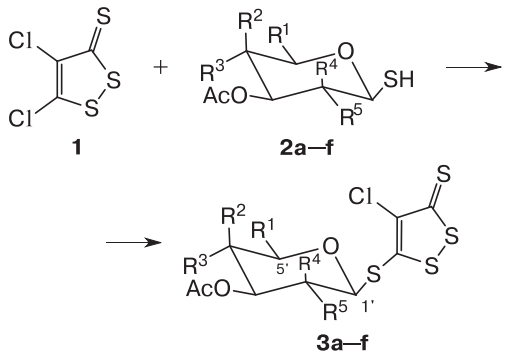
Russian Academy of Sciences showed that the conversion of natural and synthetic 1,4-naphthoquinones into *O*- and *S*-glycoside derivatives performed to increase their solubility and bioavailability leads in some cases to a significant increase in their biological activity and a decrease in toxicity.[22] It seemed promising to carry out a similar modification of the available synthon, 4,5-dichloro-1,2-dithiole-3-thione (**1**) through the nucleophilic substitution of an active chlorine atom at position 5 with a thioglycoside fragment. Available per-*O*-acetyl-1-mercapto derivatives of D-glucose, D-galactose, D-mannose, D-xylose, L-arabinose, and D-maltose[23] were chosen as the carbohydrate component.

The optimal synthesis conditions were worked out on the example of condensation of tetra-*O*-acetyl-1-thioglucopyranose **2a** with 4,5-dichloro-1,2-dithiole-3-thione (**1**) (Scheme 1). Simultaneous mixing of equimolar amounts of the reagents and a base (K_2CO_3 or Cs_2CO_3) in a solvent (acetone, benzene, and MeCN) at room temperature resulted in a strong tar formation, and the target acetylthioglucoside **3a** was isolated in a low yield of 3—5%. Conducting the condensation by gradual addition of acetylthioglucose **2a** to a solution of compound **1** in the presence of an excess of K_2CO_3 allowed us to slightly increase the yield of acetylthioglucoside **3a** to 10—13%, with the best results being obtained in MeCN as a solvent. It was noted that the presence of water in the reaction medium leads to the formation of a thin film of resinous products on the K_2CO_3 (Cs_2CO_3) surface, which hinders the contact of the reagents. To eliminate this undesirable obstacle, we added activated 4 Å molecular sieves to the reaction medium, which increased the yield of glycoside **3a** to 25—30%, but, unfortunately, the conversion of compound **1** remained incomplete. Apparently, the main part of thioglucose **2a** turned into polar resins before it has a chance to react with compound **1**. In the attempt to achieve a complete conversion of thione **1**, we used a double excess of acetylthioglucose **2a** and added K_2CO_3 in small portions simultaneously with 4 Å molecular sieves. This procedure allows to have a fresh portion of the catalyst in the reaction medium at each moment of time and to reduce the strong tar formation in this reaction. Thus, we selected the reaction conditions (reaction of thione **1** with a two-fold excess of acetylthiosaccharides **2a—f** and K_2CO_3 in the presence of 4 Å molecular sieves in anhydrous MeCN) allowing us to obtain the target acetylthioglycosides of 4-chloro-1,2-dithiole-3-thione **3a—f** in acceptable yields of 41—56% (see Scheme 1).

The structures of the new thioglycosides **3a—f** were confirmed by mass spectrometry (including high-resolution technique), IR spectroscopy, and ^1H and ^{13}C NMR spectroscopy. The synthesized compounds can be stored in the refrigerator for several years without noticeable indications of decomposition.

The cytotoxic activity of compounds **3a—f** against THP-1 human leukemia cells and JB6 Cl41 P^+ mouse epidermal cells was studied using MTS analysis[24] at the G. B. Elyakov Pacific Institute of Bioorganic Chemistry of the Far-Eastern Branch of the Russian Academy of Sciences (Table 1).

Scheme 1



Compounds **2** and **3**	R^1	R^2	R^3	R^4	R^5
a	CH_2OAc	H	OAc	H	OAc
b	CH_2OAc	OAc	H	H	OAc
c	CH_2OAc	H	OAc	OAc	H
d	H	H	OAc	H	OAc
e	H	OAc	H	H	OAc
f	CH_2OAc	H	α-d-Glc(OAc)$_4$	H	OAc

Reagents and conditions: K_2CO_3, MeCN (anhydrous), 4 Å molecular sieves.

The study of the structure—cytotoxicity relationship with respect to THP-1 human tumor cells for thioglycosides **3a—f** showed that compounds **3e** and **3f** containing arabinose and maltose residues are 1.5—2 times less active than compounds **3a—d**.

The cancer preventive activity of compounds **3a—f** against JB6 Cl41 P^+ and THP-1 cells was studied by a widely used soft agar method, with the epidermal growth factor serving as a promoter of the tumor transformation of JB6 Cl41 P^+ cells.[25—27] It was shown that compounds **3a—f** dose-dependently inhibit the tumor transformation of JB6 Cl41 P^+ cells and the formation of colonies of THP-1 cells (Tables 2 and 3).

Based on the data presented in Tables 2 and 3, we calculated the effective concentrations ($INCC_{50}$) at which compounds **3a—f** inhibited transformation or colony formation of 50% of JB6 Cl41 P^+ or THP-1 cells (Table 4). The effective concentrations $INCC_{50}$ of compounds **3a—f** varied within 0.8—15.3 μmol L^{-1} (see Table 4). It should be noted that compounds **3a—f** exhibit cancer preventive activity against transformed JB6 Cl41 P^+ cells and THP-1 tumor cells at non-cytotoxic concentrations (see Tables 1 and 4).

According to the experimental data, compounds **3a—f** inhibit tumor transformation of JB6 Cl41 P^+ cells at concentrations 7, 3, 6, 8, 5, and 4 times lower than cytotoxic ones (IC_{50}) and suppress the formation of THP-1 cell

colonies at concentrations 3, 36, 10, 70, 48, and 11 times lower than cytotoxic ones (see Tables 1 and 4).

The effect of compounds **3a—f** on AP-1-dependent transcriptional activity was studied using JB6 Cl41

Table 1. Cytotoxicity of compounds **3a—f** at various concentrations against THP-1 and JB6 Cl41 P^+ cells and the IC_{50} values of these compounds

Compound	Cell survival (in % to control)					IC_{50} /μmol L^{-1}
	0.0	12.5	25	50	100	
	/μmol L^{-1}					
	THP-1 cells					
3a	100.0±1.3	71.2*±4.8	84.1*±2.6	33.2*±3.8	7.1*±0.4	47.5
3b	100.0±1.3	86.4*±6.3	68.0*±7.1	56.9*±2.9	10.6*±0.5	54.2
3c	100.0±1.3	88.1*±5.2	71.8*±5.1	37.9*±3.4	6.9*±0.7	49.0
3d	100.0±1.3	90.9*±5.0	79.2*±6.2	51.8*±3.1	12.2*±4.0	56.3
3e	100.0±8.4	—	96.0±6.1	75.9*±7.9	48.3*±4.1	95.8
3f	100.0±3.3	98.9±4.6	82.3*±8.6	66.9*±3.2	40.6*±7.3	82.2
	JB6 Cl41 P^+ cells					
3a	100.0±4.5	98.2±3.6	79.9*±14.9	45.2*±15.5	7.5*±1.2	54.4
3b	100.0±4.5	25.0*±2.5	8.5*±1.4	—	—	8.3
3c	100.0±4.5	—	—	92.8*±2.7	23.4*±5.5	80.8
3d	100.0±4.5	89.4*±6.0	65.5*±6.2	20.1*±2.0	—	33.7
3e	100.0±4.5	48.0*±5.4	14.6*±1.8	—	—	13.7
3f	100.0±4.5	82.4*±9.3	51.7*±6.5	10.0*±4.5	—	28.0

Note. The symbol "*" marks the results significantly different from the control, $p < 0.05$.

Table 2. Cancer preventive activity of compounds **3a—f** at various concentrations against THP-1 cells

Compound	Number of colonies (in % to control)									
	0.0	0.2	0.4	0.8	1.6	3.1	3.2	6.2	12.5	25.0
	/μmol L^{-1}									
3a	100.0±6.9	—	—	—	—	106.2±10.7	—	83.5*±6.8	46.9*±8.0	19.6*±5.6
3b	100.0±13.3	98.8±10.9	100.7±10.8	70.2*±7.2	29.7*±6.7	—	—	—	—	—
3c	100.0±6.9	—	—	—	—	91.8±10.1	—	24.0*±5.5	—	—
3d	100.0±13.3	97.2±8.4	86.1*±8.8	33.6*±8.5	6.8*±2.9	—	—	—	—	—
3e	100.0±6.0	—	92.4*±4.8	93.0*±5.0	56.7*±5.5	—	19.4*±3.8	—	—	—
3f	100.0±10.7	—	—	—	—	77.7*±6.9	—	66.0*±6.5	16.2*±4.8	—

Note. The symbol "*" marks the results significantly different from the control, $p < 0.05$.

Table 3. Cancer preventive activity of compounds **3a—f** at various concentrations against JB6 C141 P^+ cells

Compound	Number of colonies of transformed JB6 C141 P^+ cells (in % to control)							
	0.0	0.8	1.6	3.1	6.2	6.3	12.5	25.0
	/μmol L^{-1}							
3a	100.0±13.9	—	—	—	—	58.9*±12.7	33.7*±9.3	15.4*±7.3
3b	100.0±10.3	99.5±8.8	70.5*±5.3	32.2*±7.9	—	4.0*±3.3	—	—
3c	100.0±13.9	—	—	—	—	68.6*±13.7	51.4*±9.3	33.6*±9.5
3d	100.0±15.2	95.3±9.8	79.7*±13.2	69.5*±19.1	—	27.3*±13.3	—	—
3e	100.0±10.3	109.2±7.1	69.4*±7.7	25.2*±6.0	—	5.4*±3.0	—	—
3f	100.0±15.2	—	—	87.5*±12.9	48.1*±10.4	—	17.5*±9.2	—

Note. The symbol "*" marks the results significantly different from the control, $p < 0.05$.

Table 4. The $INCC_{50}$ values of compounds **3a—f** with respect to the formation of colonies of THP-1 cells or tumor transformation of JB6 Cl41 P^+ cells in soft agar

Compound	$INCC_{50}$/μmol L^{-1}	
	THP-1	JB6 Cl41 P^+
3a	15.3	8.2
3b	1.5	3.0
3c	4.9	12.6
3d	0.8	4.4
3e	2.0	3.0
3f	7.7	7.4

luc-AP-1 cells with a stably expressed luciferase reporter gene controlled by the AP-1 DNA-linked sequence (Table 5).

Table 5 also shows the effect of compounds **3a—f** at various concentrations on the viability of JB6 Cl41 luc-AP-1 cells. Based on these data, it can be concluded that compounds **3a—f** at non-cytotoxic concentrations dose-dependently inhibit the basic AP-1-dependent transcriptional activity. Thus, from 90 to 100% of JB6 Cl41 luc-AP-1 cells were alive after treatment with compounds **3a—f** at the concentrations indicated in Table 5. Under these conditions, AP-1 activity in the cells was inhibited to a level of 2—66% from the control one (see Table 5). Many synthetic and natural low-molecular-weight antitumor compounds inhibit the nuclear factor AP-1.[28—35]

Table 5. The effect of compounds **3a—f** at different concentrations (*C*) on the AP-1-dependent transcriptional activity in JB6 Cl41 luc-AP-1 cells

Compound	*C* /μmol L^{-1}	AP-1-dependent activity	Cell survival
		(in % to control)	
3a	0.0	100.0±11.7	100.0±4.2
	12.5	2.1*±1.2	90.69±33.1
3b	0.0	100.0±11.7	100.0±4.2
	2.5	51.0*±2.1	102.3±2.1
	5.0	7.1*±0.2	93.4*±1.9
3c	0.0	100.0±11.7	100.0±4.2
	1.25	73.9*±1.2	102.1±3.6
	2.5	66.4*±2.6	90.9*±2.0
	5.0	39.6*±2.7	58.0*±5.0
3d	0.0	100.0±11.7	100.0±4.2
	12.5	3.4*±2.3	99.0±3.9
3e	0.0	100.0±11.7	100.0±4.2
	6.25	53.0*±3.0	107.6±5.3
	12.5	1.6*±0.2	109.9±3.7
3f	0.0	100.0±11.7	100.0±4.2
	12.5	3.2*±0.9	102.8±9.1

Note. The symbol "*" marks the results significantly different from the control, $p < 0.05$.

Therefore, the inhibition of AP-1 is at least part of the molecular mechanism of action which can explain the cancer preventive activity of compounds **3a—f**.

In conclusion, the cancer preventive effect of glycosides **3a—f** at non-cytotoxic concentrations, as well as the inhibition of the pro-carcinogenic nuclear transcription factor AP-1 by these compounds, allows considering them as potential cancer preventive drugs.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) in $CDCl_3$, ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (75 MHz) in $CDCl_3$ (compounds **3a—d,f**) and DMSO-d_6 (compound **3e**). Melting points were measured on a Boetius apparatus and were not corrected. IR spectra were recorded on a Bruker Vector-22 spectrometer (Germany) in $CHCl_3$. Mass spectra were recorded on an AMD-604S mass spectrometer with direct injection of samples into the source of ions, ionization by electron impact, energy of ionizing electrons 70 eV. High-resolution mass spectra were recorded on a Bruker Maxis Impact II instrument, electrospray ionization (ESI). The measurements were performed in positive and negative ion modes at a capillary voltages of 4500 and 3200 V, respectively. Mass scan range was m/z 50—3000 D, external or internal calibration (ESI-L Low Concentration Tunning Mix, Agilent). Solutions of compounds in methanol were syringed at a flow rate of 3 μL min^{-1}. Nitrogen was the nebulizer gas (4 L min^{-1}), interface temperature was 200 °C. Reaction progress was monitored by TLC on Silufol UV_{254} plates (Czech Republic) in a petroleum ether—ethyl acetate solvent system (1 : 1, v/v). Spots of colorless acetylthiosugars were visualized by careful heating of the plates. The absorbance of the samples was measured using a μQuant plate reader (Bio-Tek Instruments, USA). Cell colonies were counted using an Olympus CKX 31 inverted microscope (Olympus, Japan). The AP-1-dependent transcriptional activity was measured using a Luminoscan Ascent Type 392 plate reader (Labsystems, Finland).

The following materials were used in the work: cell media MEM and RPMI (both from Gibco Invitrogen Corporation, USA), penicillin/streptomycin and gentamicin (BioWhittaker, USA), L-glutamine (Mediatech, USA), fetal bovine serum (FBS) (Gemini Bio-Products, USA), epidermal growth factor (EGF) (Collaborative Research, USA), MTS reagent ([5-(3-carboxymethoxyphenyl)-3-(4,5-dimethylthiazol-2-yl)-2-(4-sulfophenyl)-2*H*-tetrazolium), and the substrate for experiments with luciferase (both from Promega, USA).

The JB6 Cl41 P^+ and JB6 Cl41 luc-AP-1 cell lines were kindly provided by Prof. Z. Dong (Hormel Institute, Austin, Minnesota, USA) and were cultured in a monolayer at 37 °C in the atmosphere containing 5% of CO_2 in nutrient medium MEM containing 5% of FBS, 2 m*M* of L-glutamine, 100 U mL^{-1} of penicillin and 100 μg mL^{-1} of streptomycin. The THP-1 cell line was obtained from the American Type Culture Collection (Rockville, USA) and was cultured at 37 °C in the atmosphere containing 5% of CO_2 in nutrient medium RPMI containing 10% of FBS, 2 m*M* of L-glutamine, 100 U mL^{-1} of penicillin and 100 μg mL^{-1} of streptomycin. The information on the THP-1 cell line is available online at http://www.atcc.org. Stock solutions of compounds **3a—f** for biological tests were

prepared in DMSO, the concentration of compounds was 20 mmol L^{-1}.

The standard error of the mean (SEM) was calculated using Microsoft Excel. The statistical computer program Statistica 6.0 for Windows (StatSoft, 2001) was used to calculate the IC_{50} and the statistical significance of the results ($p < 0.05$).

4,5-Dichloro-1,2-dithiole-3-thione (1). 3,4,5-Trichloro-1,2-dithiolium chloride[36] (1.00 g (4 mmol) was added portionwise to a solution of thioacetamide (0.31 g (4 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 1 h at room temperature, filtered through a layer of silica gel, the silica gel was washed with CH_2Cl_2, the solvent was evaporated *in vacuo*. Compound **1** (800 mg (95%) was obtained as burgundy crystals, which can be stored in a refrigerator for several years without indications of decomposition, m.p. 76 °C (*cf.* Ref. 36: m.p. 76 °C).

Synthesis of acetylated thioglycosides of dithiolthione 3a—f (general procedure). Compound **1** (102 mg, 0.50 mmol) and anhydrous MeCN (25 mL) were placed into a round bottom flask equipped with an efficient magnetic stirrer. The mixture was stirred for 1—3 min until the complete dissolution of compound **1**, followed by a portionwise addition over 20 min of finely ground freshly calcined K_2CO_3 (210 mg, 1.5 mmol), 4 Å molecular sieves (2.00 g), and acetylthiosaccharide **2a—f** (0.75 mmol). The reaction progress was monitored by TLC. Then, the reaction mixture of was diluted with anhydrous toluene (15 mL) and filtered through a low-porosity glass filter, the precipitate was washed with anhydrous toluene (15 mL) on the filter and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent petroleum ether—ethyl acetate, 1 : 1 (v/v)). The resulting acetylthioglycosides of dithiolethione **3a—f** were obtained as crystalline compounds, which are stable during prolonged storage in the dark at room temperature, readily soluble in $CHCl_3$, acetone, ethyl acetate, and DMSO, moderately soluble in EtOH and MeOH, and poorly soluble in petroleum ether, hexane, and insoluble in water.

5-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl-1′-thio)-4-chloro-1,2-dithiole-3-thione (3a). The yield was 0.148 g (56%). Dark yellow crystals, m.p. 172—174 °C. $[\alpha]_D^{20}$ −13.2° (*c*, 0.2, $CHCl_3$). R_f 0.32 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 38.36; H, 3.72; Cl, 6.71; S, 24.10. $C_{17}H_{19}ClO_9S_4$. Calculated (%): C, 38.45; H, 3.61; Cl, 6.68; S, 24.15. ^{1}H NMR, δ: 2.03, 2.06, 2.10, 2.11 (all s, 12 H, 4 OAc); 3.87 (ddd, 1 H, H(5″), $J_{4,5'}$ = 10.0 Hz, $J_{5',6a}$ = 2.2 Hz, $J_{5',6b}$ = 5.1 Hz); 4.18 (dd, 1 H, H(6a′), $J_{6,6}$ = 12.6 Hz, $J_{5,6a}$ = 2.2 Hz); 4.29 (dd, 1 H, H(6b′), $J_{6,6}$ = 12.6 Hz, $J_{5',6b}$ = 5.1 Hz); 5.14 (d, 1 H, H(1′), $J_{1,2}$ = 9.91 Hz); 5.16 (m, 1 H, H(4′)); 5.24 (m, 1 H, H(2′)); 5.32 (m, 1 H, (H(3′)). ^{13}C NMR, δ: 20.6 (CO<u>C</u>H$_3$), 20.6 (CO<u>C</u>H$_3$), 20.6 (CO<u>C</u>H$_3$), 20.8 (CO<u>C</u>H$_3$), 61.7 (C(6′)), 67.7, 69.4, 76.6, 73.2, 83.4 (C(1′)), 135.2 (CCl), 159.9 (C—S), 169.3 (CH$_3$<u>C</u>=O), 169.3 (CH$_3$<u>C</u>=O), 170.0 (CH$_3$<u>C</u>=O), 170.4 (CH$_3$<u>C</u>=O), 203.0 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 2997, 1753 (C=O), 1438, 1372, 1247 (C=S), 1106, 1065. MS, *m/z* (I_{rel} (%)): 529 $[M]^+$ (28), 330 (47), 270 (9), 210 (6), 169 (86), 128 (16), 109 (46), 100 (7), 97 (7), 81 (8), 43 (100), 32 (8). HRMS, found *m/z*: 528.9527 $[M - H]^-$; calculated for $C_{17}H_{18}ClO_9S_4$: 528.9528; found *m/z* 552.9496 $[M + Na]^+$; calculated for $C_{17}H_{19}ClNaO_9S_4$: 552.9493.

5-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-galactopyranosyl-1′-thio)-4-chloro-1,2-dithiole-3-thione (3b). The yield was 0.122 g (46%). Dark red crystals, m.p. 62—63 °C. $[\alpha]_D^{20}$ −13.6° (*c*, 0.2, $CHCl_3$). R_f 0.35 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 38.39; H, 3.75; Cl, 6.73; S, 24.18. $C_{17}H_{19}ClO_9S_4$. Calculated (%): C, 38.45; H, 3.61; Cl, 6.68; S, 24.15. ^{1}H NMR, δ: 2.01, 2.07, 2.12, 2.20 (all s, 12 H, 4 OAc); 4.09 (m, 1 H, H(5′)); 4.14 (dd, 1 H, H(6a′), $J_{5',6a'}$ = 5.9 Hz, $J_{6a',6b'}$ = 11.4 Hz); 4.21 (dd, 1 H, H(6b′); $J_{5',6b'}$ = 6.9 Hz, $J_{6a,6b}$ = 11.4 Hz); 5.11 (d, 1 H, H(1′); $J_{1',2'}$ = 10.1 Hz); 5.13 (dd, 1 H, H(3′), $J_{2',3'}$ = 9.8 Hz, $J_{3',4'}$ = 3.3 Hz); 5.45 (t, 1 H, H(2′), $J_{2',3'}$ = 9.8 Hz, $J_{1',2'}$ = = 10.1 Hz); 5.51 (dd, 1 H, H(4′); $J_{3',4'}$ = 3.3 Hz; $J_{4',5'}$ = 0.9 Hz). ^{13}C NMR, δ: 20.6, 20.7, 20.7, 20.8 (4 OAc), 61.3 (C(6′)), 66.6, 66.8, 71.3, 75.4, 83.8 (C(1′)), 134.9 (CCl), 160.4 (C—S), 169.5, 169.9, 170.0, 170.3 (4 C=O), 202.9 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 2998, 1754 (C=O), 1441, 1371, 1247 (C=S), 1153, 1084, 1061. MS, *m/z* (I_{rel} (%)): 529 $[M]^+$ (19), 330 (43), 270 (11), 169 (85), 128 (15), 109 (45), 100 (8), 97 (8), 81 (6), 43 (100), 32 (6). HRMS, found *m/z*: 528.9529 $[M - H]^-$; calculated for $C_{17}H_{18}ClO_9S_4$: 528.9528; found *m/z* 552.9494 $[M + Na]^+$; calculated for $C_{17}H_{19}ClNaO_9S_4$: 552.9493.

5-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-mannopyranosyl-1′-thio)-4-chloro-1,2-dithiole-3-thione (3c). The yield was 0.123 g (47%). Dark yellow crystals, m.p. 196—198 °C. $[\alpha]_D^{20}$ −24.4° (*c*, 0.2, $CHCl_3$). R_f 0.31 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 38.42; H, 3.65; Cl, 6.63; S, 24.19. $C_{17}H_{19}ClO_9S_4$. Calculated (%): C, 38.45; H, 3.61; Cl, 6.68; S, 24.15. ^{1}H NMR, δ: 2.00, 2.07, 2.10, 2.24 (all s, 12 H, 4 OAc); 3.85 (m, 1 H, H(5′)); 4.19 (dd, 1 H, H(6a′), $J_{5',6a'}$ = 2.4 Hz, $J_{6a',6b'}$ = 12.5 Hz); 4.31 (dd, 1 H, H(6b′), $J_{5',6b'}$ = 6.1 Hz, $J_{6a,6b}$ = 12.5 Hz); 5.13 (dd, 1 H, H(3′), $J_{2',3'}$ = 3.5 Hz, $J_{3',4'}$ = 10.1 Hz); 5.31 (t, 1 H, H(4′), $J_{3',4}$ = 10.1 Hz, $J_{4',5'}$ = 10.0 Hz); 5.41 (d, 1 H, H(1′), $J_{1',2'}$ = = 0.98 Hz); 5.67 (dd, 1 H, H(2′), $J_{1',2'}$ = 0.98 Hz, $J_{2',3'}$ = 3.5 Hz). ^{13}C NMR, δ: 20.5, 20.6, 20.7, 20.9 (4 CO<u>C</u>H$_3$), 62.4 (C(6′)), 65.1, 69.5, 71.3, 77.1, 82.1 (C(1′)), 134.5 (CCl), 160.7 (C—S), 169.5, 169.8, 169.9, 170.4 (4 C=O), 202.9 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 2995, 1761 (C=O), 1452, 1368, 1222 (C=S), 1065, 1044. MS, *m/z* (I_{rel} (%)): 529 $[M]^+$ (15), 331 (34), 270 (4), 211 (6), 183 (4), 169 (76), 142 (8), 127 (17), 109 (46), 97 (8), 81 (7), 43 (100). HRMS, found *m/z*: 528.9530 $[M - H]^-$; calculated for $C_{17}H_{18}ClO_9S_4$: 528.9528; found *m/z*: 552.9504 $[M + Na]^+$; calculated for $C_{17}H_{19}ClNaO_9S_4$: 552.9493.

5-(2′,3′,4′-Tri-*O*-acetyl-β-D-xylopyranosyl-1′-thio)-4-chloro-1,2-dithiole-3-thione (3d). The yield was 0.112 g (49%). Orange crystals, m.p. 155—156 °C. $[\alpha]_D^{20}$ −31.4° (*c*, 0.2, $CHCl_3$). R_f 0.40 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 36.53; H, 3.35; Cl, 7.81; S, 28.01. $C_{14}H_{15}ClO_7S_4$. Calculated (%): C, 36.64; H, 3.29; Cl, 7.72; S, 27.95. ^{1}H NMR, δ: 2.11, 2.13, 2.14 (all s, 9 H, 3 OAc); 3.68 (dd, 1 H, H(5a′), $J_{4',5a'}$ = = 6.4 Hz; $J_{5a',5b'}$ = 12.4 Hz); 4.40 (dd, 1 H, H(5b′), $J_{4',5b'}$ = = 4.0 Hz, $J_{5a',5b'}$ = 12.4 Hz); 4.96 (m, 1 H, H(4′)); 5.09 (t, 1 H, H(2′), $J_{1',2'}$ = 6.1 Hz, $J_{2',3'}$ = 6.2 Hz); 5.22 (t, 1 H, H(3′), $J_{2',3'}$ = 6.2 Hz); 5.48 (d, 1 H, H(1′) $J_{1',2'}$ = 6.1 Hz). ^{13}C NMR, δ: 20.4, 20.4, 20.5 (3 CO<u>C</u>H$_3$), 64.6, 67.5, 68.6, 70.3, 82.4 (C(1′)), 132.6 (CCl), 164.0 (C—S), 169.2, 169.3, 169.5 (3 CH$_3$<u>C</u>=O), 203.4 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 2996, 1760 (C=O), 1438, 1372, 1246 (C=S), 1194, 1089. MS, *m/z* (I_{rel} (%)): 457 $[M]^+$ (23), 259 (40), 199 (15), 157 (33), 139 (42), 97 (50), 69 (6), 43 (100), 32 (6). HRMS, found *m/z*: 456.9317 $[M - H]^-$; calculated for $C_{14}H_{14}ClO_7S_4$: 456.9316; found *m/z*: 480.9284 $[M + Na]^+$; calculated for $C_{14}H_{15}ClNaO_7S_4$: 480.9281.

5-(2′,3′,4′-Tri-*O*-acetyl-β-L-arabinopyranosyl-1′-thio)-4-chloro-1,2-dithiole-3-thione (3e). The yield was 0.094 g (41%). Reddish brown crystals, m.p. 235—237 °C. $[\alpha]_D^{20}$ −20.0° (*c*, 0.2, $CHCl_3$). R_f 0.43 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 36.57; H, 3.38; Cl, 7.88; S, 27.89. $C_{14}H_{15}ClO_7S_4$. Calculat-

ed (%): C, 36.64; H, 3.29; Cl, 7.72; S, 27.95. ^{1}H NMR, δ: 2.13, 2.13, 2.15 (all s, 9 H, 3 OAc); 3.82 (dd, 1 H, H(5a′), $J_{4',5a'}$ = = 3.0 Hz; $J_{5a',5b'}$ = 12.3 Hz); 4.22 (dd, 1 H, H(5b′), $J_{4',5b'}$ = = 6.0 Hz, $J_{5a',5b'}$ = 12.3 Hz); 5.24 (dd, 1 H, H(3′), $J_{2',3'}$ = 7.1 Hz, $J_{3',4'}$ = 3.2 Hz); 5.33 (t, 1 H, H(2′), $J_{1',2'}$ = 5.9 Hz, $J_{2',3'}$ = 7.1 Hz); 5.35 (m, 1 H, H(4′)); 5.41 (d, 1 H, H(1′) $J_{1',2'}$ = 5.9 Hz). ^{13}C NMR, δ: 20.7, 20.7, 20.9 (3 CO<u>C</u>H$_3$), 63.9, 66.2, 68.5, 68.9, 83.7 (C(1′)), 134.5 (CCl), 161.7 (C—S), 169.3, 169.5, 169.9 (3 CH$_3$<u>C</u>=O), 203.0 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 2997, 1753 (C=O), 1438, 1372, 1247 (C=S), 1106, 1065. MS, *m/z* (I_{rel} (%)): 457 $[M]^+$ (33), 259 (69), 199 (12), 157 (34), 139 (70), 134 (4), 115 (6), 97 (75), 69 (11), 43 (100). HRMS, found *m/z*: 456.9315 $[M - H]^-$; calculated for $C_{14}H_{14}ClO_7S_4$: 456.9316; found *m/z*: 480.9289 $[M+Na]^+$; calculated for $C_{14}H_{15}ClNaO_7S_4$: 480.9281.

5-[2′,3′,6′-Tri-*O*-acetyl-4′-*O*-(2″,3″,4″,6″-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl-1′-thio)]-4-chloro-1,2-dithiole-3-thione (3f). The yield was 0.229 g (56%). Dark orange crystals, m.p. 97—98 °C. $[\alpha]_D^{20}$ +2.4° (*c*, 0.2, $CHCl_3$). R_f 0.30 (petroleum ether—ethyl acetate, 1 : 1). Found (%): C, 42.46; H, 4.21; Cl, 4.40; S, 15.71. $C_{29}H_{35}ClO_{17}S_4$. Calculated (%): C, 42.51; H, 4.31; Cl, 4.33; S, 15.65. ^{1}H NMR, δ: 2.01, 2.04, 2.04, 2.05, 2.07, 2.11, 2.15 (all s, 21 H, 7 OAc); 3.86 (m, 1 H, H(5′); 3.97 (m, 1 H, H(5″)); 4.05 (m, 1 H, (4′)); 4.08 (m, 1 H, H(6′)); 4.24 (m, 1 H, H(6″)); 4.26 (m, 1 H, H(6′)); 4.51 (dd, 1 H, *J* = 2.5 Hz; *J* = 12.4 Hz); 4.87 (dd, 1 H, H(2″) *J* = 4.0 Hz; *J* = 10.6 Hz); 5.09 (m, 1 H, H(4′)); 5.10 (m, 1 H, (2′)); 5.20 (d, 1 H, (1′), $J_{1',2'}$ = 10.0 Hz); 5.38 (m, 2 H, H(3′), H(3″)); 5.45 (d, 1 H, H(1″), $J_{1'',2''}$ = 4.0 Hz). ^{13}C NMR, δ: 20.5, 20.6, 20.6, 20.7, 20.8, 20.9, 20.9 (7 CO<u>C</u>H$_3$), 61.5. 62.6, 68.0, 68.8, 69.2, 70.0, 70.2, 72.3, 75.7, 76.8, 82.9 (C(1)), 95.9 (C(1)), 135.1 (CCl), 159.9 (C—S), 169.4 169.5, 170.0, 170.2, 170.3, 170.5, 170.6 (7 <u>C</u>OCH$_3$), 203.0 (C=S). IR ($CHCl_3$), ν/cm^{-1}: 3018, 1754 (C=O), 1441, 1369, 1247 (C=S), 1044. MS, *m/z* (I_{rel} (%)): 818 $[M]^+$ (16), 618 (11), 575 (7), 558 (18), 531 (3), 498 (3), 330 (60), 271 (22), 210 (23), 169 (100), 138 (35), 109 (75), 99 (22), 81 (18), 43 (70). HRMS, found *m/z*: 817.0376 $[M - H]^-$; calculated for $C_{29}H_{34}ClO_{17}S_4$: 817.0373; found *m/z*: 841.0342 $[M + Na]^+$; calculated for $C_{29}H_{35}ClNaO_{17}S_4$: 841.0338.

Study of the cytotoxic activity of compounds 3a—f. The effect of compounds **3a—f** on cell viability was investigated using the MTS assay. The THP-1 cells were cultured for 12 h in 96-well plates (6000 cells per well) in nutrient medium (50 μL per well) containing 10% of FBS. Then 50 μL of the medium containing 10% of FBS and test compound at various concentrations was added to each well, and the plates with cells were incubated for 22 h. Then, 20 μL of MTS reagent was added to each well and after 2 h the absorbance of the formed formazan was measured spectrophotometrically at 492 and 690 nm as a reference wavelength. The JB6 Cl41 P^+ or JB6 Cl41 luc-AP-1 cells were cultured for 12 h in 96-well plates (6000 cells per well) in nutrient medium MEM (100 μL per well) containing 10% of FBS. Then the medium was removed, followed by the addition of 100 μL of fresh medium containing 10% of FBS and test compound at various concentrations to each well. The cells were incubated for 22 h, then 20 μL of MTS reagent was added to each well and after 2 h the absorbance of the formed formazan was measured spectrophotometrically at 492 and 690 nm as a reference wavelength. Cell viability was calculated as the percentage of the absorption intensity in the experimental wells to the absorption intensity in the control wells. The data are presented in Table 1 as a mean value ± standard error of the mean (SEM) for three samples in two independent experiments.

Cancer preventive effect of glycosides 3a—f was studied by the soft agar method using transformed JB6 Cl41 P^+ mouse epidermal cells or THP-1 human leukemia cells. Epidermal growth factor EGF (10 ng mL^{-1}) was used to stimulate the neoplastic transformation of JB6 Cl41 P^+ cells. The experiments were carried out in six-well culture plates. The cells ($8 \cdot 10^3$ in 1 mL) were treated with the test compounds at various concentrations in 1 mL of 0.33% agar in BME cell medium containing 10% of FBS over 3 mL of 0.5% agar in BME medium containing 10% of FBS and test compounds at various concentrations. The plates were incubated for seven days at 37 °C in the atmosphere containing 5% of CO_2, after which the cell colonies were counted. The cancer preventive activity of compounds **3a—f** was calculated as the percentage ratio of the number of cell colonies in the experimental wells to the number of cell colonies in the control wells. The data are presented in Tables 2 and 3 as a mean value ± standard error of the mean (SEM) for three samples in two independent experiments.

Study of the effect of compounds 3a—f on the activity of the nuclear factor AP-1. The ability of glycosides **3a—f** to influence the AP-1-dependent transcriptional activity in JB6 Cl41 luc-AP-1 cells was assessed using the luciferase method. A suspension of JB6 Cl41 luc-AP-1 cells ($6 \cdot 10^3$) in 100 μL of medium MEM containing 5% of FBS was added to each well of a 96-well plate. The plate with cells was incubated for 12 h, after which the cells were treated with the test compounds at various concentrations in 100 μL of fresh 5% medium FBS/MEM. After incubation of the cells with the test compounds for 24 h, the medium was removed from the wells and the cells were extracted for 1 h at room temperature using a lysis buffer solution (0.1 *M* potassium phosphate buffer solution (pH 7.8) containing 1% of Triton X-100, 1 m*M* DTT, 2 m*M* EDTA), 100 μL per well. Then 30 μL of lysate from each well was transferred into the corresponding wells of the plate for luminescence analysis, added 100 μL of buffer solution containing luciferin (0.47 m*M* D-luciferin; 20 m*M* tricin; 1.07 m*M* $(MgCO_3)_4 \cdot Mg(OH)_2 \cdot 5H_2O$; 2.67 m*M* $MgSO_4 \cdot 7H_2O$; 3.33 m*M* DTT; 0.53 m*M* ATP; 0.27 m*M* CoA; 0.1 m*M* EDTA (pH 7.8)) and luciferase activity was measured. The AP-1-dependent transcriptional activity was calculated as the percentage ratio of the luminescence intensity in the experimental wells to the luminescence intensity in the control wells. The data are presented in Table 5 as a mean value ± standard error of the mean (SEM) for three samples in two independent experiments.

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