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The synthesis of thioglucosides substituted 1,4-naphthoquinones and their conversion in oxathiane fused quinone-thioglucoside conjugates

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Dedicated to Prof. Oleg A. Rakitin on the occasion of his 65th anniversary

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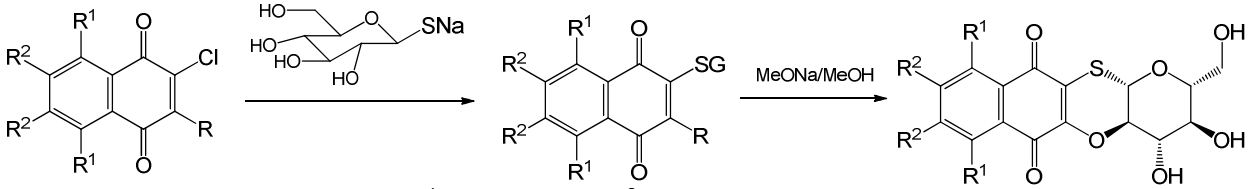
Abstract

In this paper we describe a methodology for the preparation of thioglucosides of substituted 1,4-naphthoquinones *via* condensation of related chloronaphthoquinones with the sodium salt of 1-thio-β-D-glucopyranose in acetone-MeOH solution and subsequent base-catalytic conversion of these mono- and dithioglucosides in the linear tetracyclic quinone-carbohydrate conjugates.



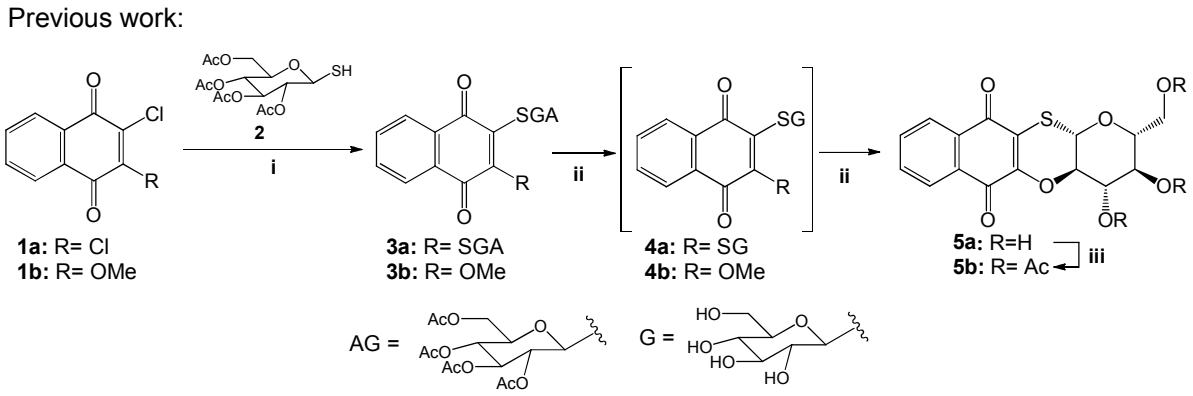
R= Cl, OMe, SG; R^1 = H, OH, OMe; R^2 = H, Me, Cl; SG = 1-thioglucopyranosyl

Keywords: 1-Thioglucose sodium salt, 1,4-naphthoquinones, thioglucosides, heterocyclisation.

Introduction

The 1,4-napthoquinones are widely distributed in nature and occur in animals, plants and microorganisms[1]. This group of compounds exhibits antibacterial,[2] cardioprotective[3] and anticancer activities[4-5] and provide structures regarded as perspectives in medicinal chemistry. Quinones exert their actions through the generation of reactive oxygen species and modulation of redox signaling radical reactions: as prooxidants; as antioxidants and as electrophiles, forming covalent bonds with tissue nucleophiles.[6] That broad spectrum of biological activity renders them interesting leads for the development of novel medicines.[7] Naphthoquinones often possess poor solubility which hampered their practical use. The conjugation of naphthoquinones with non-toxic carbohydrates is one of the best successful way for improving their solubility. Also, conjugation of naphthoquinones with carbohydrates led to the novel structures with new types of biological activity.[8-11]

In the course of our drug research project we developed an effective method for preparation of naphthoquinone acetylthioglucosides by the condensation of available substituted chloroquinones **1a,b** with tetra-O-acetyl-1-thio-β-D-glucopyranose (**2**) (AGSH) and obtained related naphthoquinone acetylglucosides **3a,b**. The acetylglucoside naphthoquinones **3a,b** readily were deacetylated with MeONa/MeOH and led the water soluble thioglucosides **4a,b**. However under these base conditions thioglucosides **4a,b** immediately converted in the insoluble quinone-sugar tetracyclic conjugate **5a** in good yield[12] (Scheme 1). Recently, this protocol was successfully used to prepare quinone-sugar tetracyclic conjugates based on quinone **1b** with acetylated 1-mercaptosugars of D-galactose, D-mannose, D-xylose, L-arabinose and D-maltose.[13] The obtained sugar-quinone tetracycles were converted in acetyl derivatives by the treatment Ac_2O/Py. Both synthesized tetracyclic quinone conjugates and their acetylated tetracylic derivatives were active *in vitro* against human promyelocytic leukemia HL-60 in 1.0–5.0 μM concentrations, while starting acyclic acetylglycosides were less active ~10–100 times.[14]

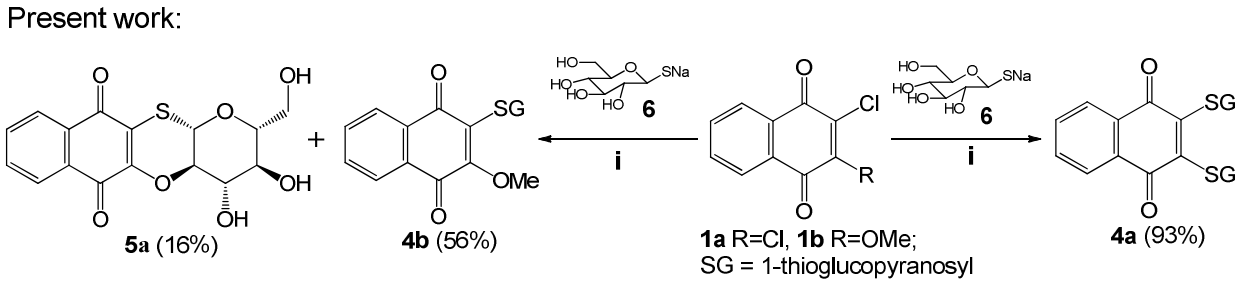


Scheme 1. Reagents and conditions: (i) K_2CO_3, acetone, r,t.; (ii) MeONa/MeOH, r.t.; (iii) Ac_2O/Py, rt.

Results and Discussion

In present work we describe a methodology for the preparation of base-sensitive thioglucosides of various 1,4-naphthoquinones by the condensation of substituted chloronapthoquinones with the sodium salt of 1-thio-β-D-glucopyranose (**6**) and a base-catalytic conversion of these thioglucosides to tetracyclic quinone-carbohydrate conjugates. The thioglucose sodium salt **6** is the good nucleophile and a weak base, therefore it

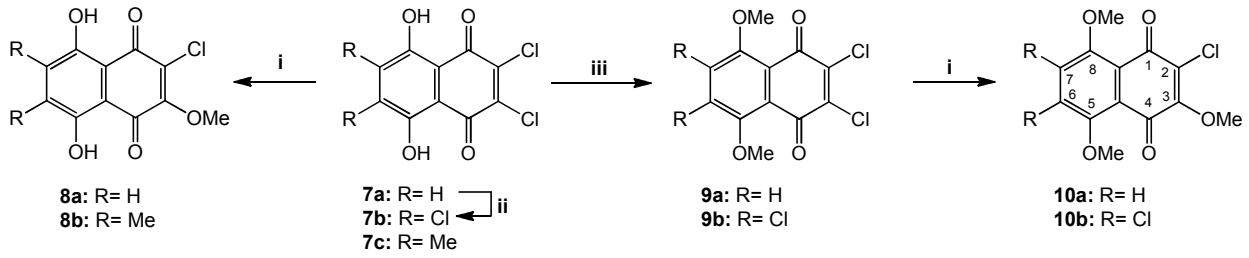
can be used for direct preparation of naphthoquinone thioglucosides without base-catalyzed deacetylation procedure.



Scheme 2. Reagents and conditions: (i) acetone/MeOH, rt.;

The study was performed on substituted 2,3-dichloro- and 2-methoxy-3-chloro-1,4-naphthoquinones, which were converted in naphthoquinone mono- and dithioglucosides (Schemes 2, 4 and 6). Initially, we examined the utility of 1-thioglucose **6** on model compounds **1a,b**. We found that chloroquinones **1a,b** were only slightly soluble in MeOH. In order to improve quinone solubility the mixture of methanol-acetone was used in subsequent experiments. The treatment of chloromethoxyquinone **1b** with equimolar amount of thioglucose sodium salt **6** at r.t. for 1.5 h gave a mixture of methoxynaphthoquinone thioglucoside **4b** (56% yield) and quinone tetracycle **5a** (16% yield) under 79% conversion of chloromethoxyquinone **1b** (Scheme 2). Condensation of the dichloronaphthoquinone **1a** (0.30 mM) with thioglucose sodium salt **6** (0.75 mM) proceeded easily within 30 min, and led to dithioglucoside **4a** in an excellent 93% yield.

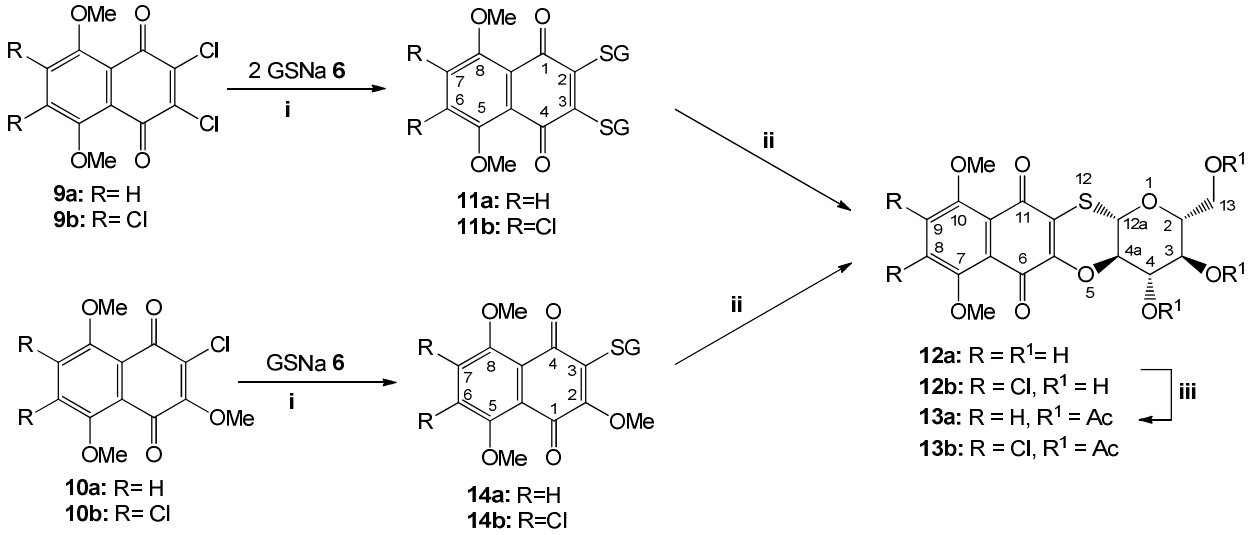
The structures of the other starting quinones were chosen in such manner, that the heterocyclization of both diglycoside and related methoxymonoglucoside gave the same reaction product. The key dichloroquinones **7a,c** were prepared by Friedel–Crafts condensation of dichloromaleic anhydride with suitable 1,4-hydroquinones[15,16]. The tetrachloroquinone **7b** was obtained following literature procedure[17]. Methylation[15] of quinones **7a,b** by MeI/Ag_2O in $CHCl_3$ solution gave 5,8-dimethoxychloroquinones **9a,b** in good 60–80% yield (Scheme 3). Partial substitution of one chlorine atom in 2,3-dichloroquinones **7a** and **9a,b** was achieved according to the literature[15] by treatment with AcONa/MeOH at reflux and led to methoxychloroquinones **8a**, **10a,b** in good yields (75–85%). Quinone **7c** reacted with AcONa/MeOH only by heating in an autoclave at 95 °C for 8 h and gave the desired product **8b** in a low 29% yield.



Scheme 3. Reagents and conditions: (i) AcONa/MeOH, reflux; (ii) HCl/MnO_2, AcOH, reflux; (iii) MeI/Ag_2O, $CHCl_3$, rt.

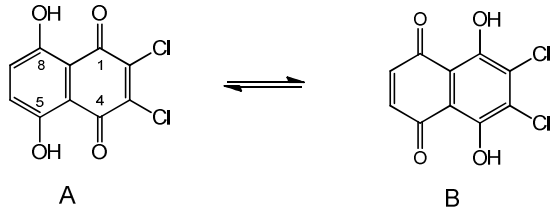
The condensation of dichloronaphthoquinones **9a,b**, bearing chloro- and methoxysubstituents in quinoid core led to dithioglucosides **11a,b** with 89–94% yield. These dithioglucosides **11a,b** under treatment by MeONa/MeOH were easily converted within 30-60 min in the tetracyclic conjugates **12a,b** in good yields

83–86%. The substitution of chloromethoxyquinones **10a** with equimolar ratio of thioglucose salt **6** proceeded in acetone/MeOH solution in 1 h and gave monoglucoside **14a** in 80% yield. Under these conditions the trichloromethoxynaphthoquinone **10b** led to monoglucoside **14b** (74%) and related tetracyclic conjugate **12b** (7%). Under MeONa/MeOH treatment, the monoglucosides **14a,b** were readily converted to tetracycles **12a,b** in 75–81% yields. Tetracylic quinones **12a,b** were easily acetylated by Ac_2O/Py and gave acetyl derivatives **13a,b** in good yields 84–85%.



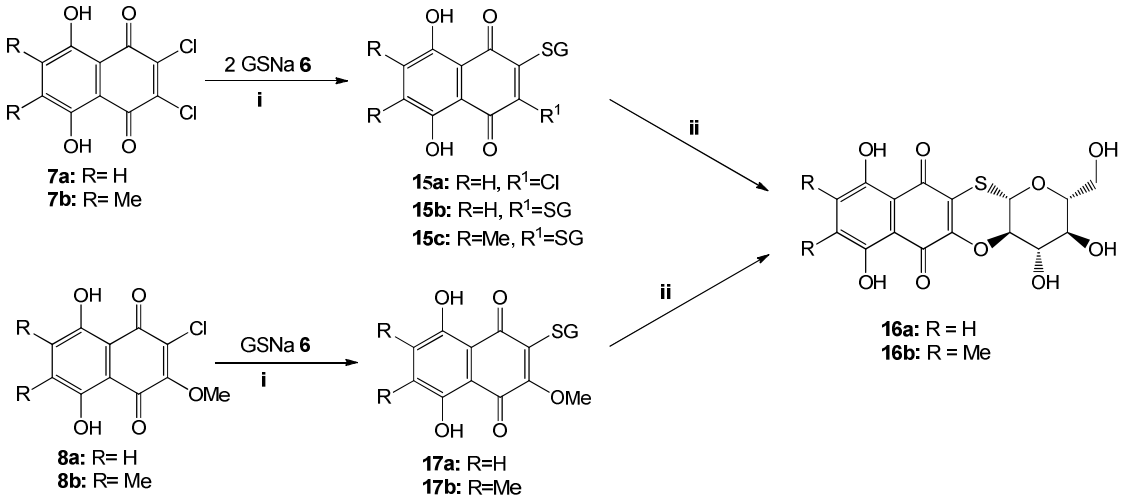
Scheme 4. Reagents and conditions: (i) acetone/MeOH, r.t.; (ii) MeONa/MeOH, r.t.; (iii) Ac_2O/Py, rt.

The final part of the study was carried out on the 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) derivatives **7a,b** and **8a,b**. It is known that naphthazarin exists in various tautomeric forms that react with the formation of different reaction products[15].



Scheme 5. Dichloronaphthazarin **7a** tautomeric equilibrium.

To suppress the addition of thioglucose to the quinone ring of dichloronaphthazarin tautomer B (Scheme 5), the dichloroquinone **7a** (0.50 mM) was condensed with reduced amount of thioglucose salt **6** (0.91 mM) in acetone-methanol solution for 1 h and led to mixture of chloronaphthazarin thioglucoside **15a** (21%) and naphthazarin bisthioglucoside **15b** (69 %) (Scheme 6). Dichlorodimethylnaphthazarin **7b** (0.50 mM) reacted with an excess of thioglucose salt **6** (1.261 mM) in only 18 h and gave the dithioglucoside dimethylnaphthazarin **15c** in an excellent 95% yield. It can be assumed that the reduced reactivity of dichlorodimethylnaphthazarin **7b** in nucleophilic substitution reaction is due to the electron donor effect of two methyl groups on tautomeric equilibrium of naphthazarin core.



Scheme 6. Reagents and conditions: (i) acetone/MeOH, r.t.; (ii) MeONa/MeOH, rt.

The substitution of chloromethoxynaphthoquinone **8a** (0.40 mM) with thioglucose salt **6** (0.50 mM) proceed in acetone/MeOH solution in 1.5 h until the disappearance of starting quinone **8a** and formation of two polar products with R_f 0.34 and R_f 0.10. The first compound with R_f 0.34 was monoglucoside **17a** (80%) and the polar product with R_f 0.10 was bisglucoside **15c** (15%). The bisglucoside **15c** was formed as a result of the replacement of the methoxy group in quinone **8a**. In these conditions the trichloromethoxynaphthoquinone **8b** led to the formation of monoglucoside **17b** (74%) and related tetracycle conjugate **16b** (7%). Under the base treatment by MeONa/MeOH both monoglucosides **17a,b** were readily converted in tetracycles **16a,b** with yields 75–81%. It is evident, that tetracyclic quinone-glucoside conjugates of **12a,b** and **16a,b** were formed from methoxymonoglucosides **14a,b**, **17a,b** and bisglucosides **11a,b**, **15b,c** through intramolecular nucleophilic substitution of the methoxyl group or 1-thioglucose residue. This process proceeds with retention of the configuration of all asymmetric centers of the carbohydrate portion.

The structures of new compounds were proved by NMR, IR spectroscopy and HR mass spectrometry. Attachment of thioglucoside to naphthoquinone core in the new compounds was evidenced by appearance of the signals of thioglucose moiety together with the retention of other signals of aromatic protons, phenolic α-hydroxyl groups of naphthazarin nucleus and the signals of methyl and methoxyl groups. The 1',2'-trans(β)-configuration of thioglucoside bond in naphthoquinone thioglucosides **4a,b**, **11a,b**, **14a,b**, **15a,b,c** and **17a,b** was confirmed by the value of anomeric proton doublets ($J_{1',2'}$ = 8.4–10.0 Hz) in the ^{1}H NMR spectra. Spectral data of new and known starting chloronaphthoquinones **7a,b,c**–**10a,b** were in a good agreement with their proposed structures.

Conclusions

A novel and facile method for synthesis of base-sensitive di- and monothioglucosides of various 1,4-naphthoquinones by the condensation of substituted chloronapthoquinones with the sodium salt of 1-thio-β-D-glucopyranose was developed. Both naphthoquinone di- and methoxymonothioglucosides under MeONa/MeOH treatment were readily converted in linear tetracyclic quinone-carbohydrate conjugates in good yields.

Experimental Section

General. Melting points (uncorrected) were measured with a Boetius apparatus. IR spectra were recorded on Bruker Vector-22 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE-500 and Bruker AVANCE-700 at frequencies 500 and 700 MHz for ^{1}H spectra and 125 and 176 MHz for ^{13}C spectra, respectively. 2D NMR experiments {^{1}H–^{1}H} COSY, {^{1}H–^{13}C} HMBC-qs, and {^{1}H–^{13}C} HSQC were used where necessary in assigning NMR spectra. Spin-spin coupling constants (*J*) were reported in hertz (Hz). Chemical shifts were referenced to TMS (δ=0.00 ppm). EI mass spectra and high resolution mass spectra were recorded on AMD-604S instrument at 70 eV. ESI mass spectra and ESI high resolution mass spectra were recorded on an Agilent 651 Q-TOF LC/MS instrument. 1-Thio-β-D-glucopyranose sodium salt (Chemapol) was used. Silufol UV-VIS TLC plates (Chemapol) treated vapor of hydrochloric acid were used for analytical TLC. Preparative TLC was performed on silica gel 60 (Merck, 40–63 μm). TLC was developed in system A: hexane–benzene–acetone, 2:1:1, system B: benzene–ethylacetate-methanol, 2:1:1 and system C: benzene–ethylacetate-methanol, 7:4:1.

Condensation of 2-chloro-3-methoxynaphthoquinone 1b with thioglucose sodium salt 6. 2-Chloro-3-methoxynaphthoquinone **1b** 111 mg (0.50 mM) was dissolved in acetone (10 mL) and MeOH (10 mL), β-D-thioglucopyranose sodium salt (**6**) 110 mg (0.50 mM) was added. The resulting mixture was stirred during 1.5 h at room temperature until the consumption of thioglucose **6** and conversion of the starting quinone **1b** in the new yellow compound with R_f 0.56 (B). During the reaction, the formation of a brown precipitate was observed. The precipitate was filtered off, washed with water, acetone, dried in a vacuum and identified as **(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Hydroxymethyl-3,4,-dihydroxy-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (5a)**. Yield 28 mg (16%), orange powder, mp 350–351 °C (Lit. data[12], mp 350–351 °C). The filtrate was evaporated in vacuum and the residue was subjected to preparative TLC (system B) and yielded starting compound **2-chloro-3-methoxynaphthoquinone 1b** (23 mg, 21%) and **3-(β-D-glucopyranosyl-1-thio)-2-methoxynaphthalene-1,4-dione (4b)**. Yield 108 mg (56%), brown solid, mp 96–99 °C. R_f 0.56 (B). ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.09 (m, 3H, H-2', 2H-4', H-5',), 3.22 (m, 1H, H-3'), 3.34 (m, 1H, H-6'), 3.53 (m, 1H, H-6'), 4.11 (s, 3H, ArOMe), 4.33 (t, 1H, *J* 5.7 Hz, C$^{6'}$H$_2$OH), 4.93 (d, 1H, *J* 4.4 Hz, C$^{4'}$HOH), 5.10 (d, 1H, *J* 4.0 Hz, C$^{3'}$HOH), 5.29 (d, 1H, *J* 9.7 Hz, H-1'), 5.46 (d, 1H, *J* 6.2 Hz, C$^{2'}$HOH), 7.82 (m, 2H, ArH), 7.95 (m, 1H, ArH), 7.97 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 60.9 (C-6'), 61.0 (MeO), 70.0 (C-4'), 74.5 (C-2'), 78.2 (C-3'), 81.4 (C-5'), 82.6 (C-1'), 126.0, 130.9, 131.2, 132.0, 133.9, 157.8, 178.4, 182.5. IR (KBr): 3435 (OH), 2923, 1660 (C=O), 1591, 1555, 1441, 1385, 1334, 1254, 1215, 1142, 1075, 1046, 1020, 919 cm^{-1}. MS (ESI): *m/z* 405 [M+Na]. HRMS (ESI): calcd for $C_{17}H_{18}NaO_8S$ 405.0615, found 405.0622.

Condensation of 2,3-dichloronaphthoquinone (1a) with thioglucose sodium salt 6. 2,3-Dichloronaphthoquinone (**1a**) 68 mg (0.35 mM) was dissolved in acetone (6 mL) and MeOH (6 mL) and glucose sodium salt **6** 163 mg (0.75 mM) was added. The resulting mixture was stirred during 1.5 h at room temperature until the conversion of starting quinone **1a** with R_f 0.90 (B) into a new yellow compound with R_f 0.30 (B). Inorganic salts were filtered off, and the precipitate was washed with acetone. The combined filtrate was evaporated in vacuum, and the residue was subjected to preparative TLC, yielded 2,3-bisglucoside **2,3-di(β-D-glucopyranosyl-1-thio)naphthalene-1,4-dione (4a)**. Yield 152 mg (93%), yellow powder, R_f 0.30 (B), mp >360 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.04 (m, 2H, 2 × H-5'), 3.10 (m, 2H, 2 × H-4'), 3.14 (m, 2H, 2 × H-2'), 3.33 (m, 2H, 2 × H-6'), 3.46 (m, 2H, 2 × H-6'), 4.26 (m, 2H, 2 × C$^{6'}$H$_2$OH), 4.93 (m, 2H, 2 × C$^{4'}$HOH), 5.10 (m, 2H, 2 × C$^{3'}$HOH), 5.37 (d, 2H, *J* 9.4 Hz, 2 × H-1'), 5.49 (m, 2H, 2 × C$^{2'}$HOH), 7.79 (m, 2H, H-6, H-7), 7.94 (m, 2H, H-5, H-8). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 60.7 (C-6'), 69.9 (C-4'), 74.9 (C-2'), 78.2 (C-3'), 81.6 (C-5'), 83.9 (C-1'),

126.5, 132.6, 133.7, 146.5, 178.7 (C=O). IR (KBr): 3425 (OH), 2926, 1658 (C=O), 1617, 1414, 1275, 1181, 1141, 1075, 1049 cm^{-1}. MS (ESI): *m/z* 569 [M+Na]. HRMS (ESI): calcd for $C_{22}H_{26}NaO_{12}S_2$ 569.0758, found 569.0752.

2-Chloro-5,8-dihydroxy-3-methoxynaphtalene-1,4-dione (**8a).** 2,3-Dichloroquinone **7a** 259 mg (1.00 mM), dry AcONa 790 mg (9.61 mM) and dry methanol (60 mL) was stirred at reflux 0.5 h. Reaction mixture was cooled, was acidified in drops with conc. HCl, inorganic salts were filtrated off, the precipitate was washed with acetone and filtrate was evaporated in vacuum. The crystallization of residue from MeOH gave 185 mg (72%) of 2-chloro-5,8-dihydroxy-3-methoxynaphtalene-1,4-dione **(8a)**; red solid, mp 160–162°C, (lit. data[17] 161–162°C).

2-Chloro-5,8-dihydroxy-3-methoxy-6,7-dimethylnaphtalene-1,4-dione (**8b).** 2,3-Dichloroquinone **7b** 287 mg (1.00 mM), dry AcONa 790 mg (9.61 mM) and dry methanol (100 mL) was stirred in stainless autoclave at 95 °C within 5 h. The reaction mixture was cooled, acidified in drops with conc. HCl, inorganic salts were filtrated off, and the filtrate was evaporated in vacuum. The residue was subjected to preparative TLC on silica gel, eluting with system A, to give polar red fraction with R_f 0.36 (A). The crystallization of the fraction from MeOH yielded 82 mg (29%) of 2-chloro-5,8-dihydroxy-3-methoxy-6,7-dimethylnaphtalene-1,4-dione **(8b)**; red solid, mp 188–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H, ArMe), 2.27 (s, 3H, ArMe), 4.27 (s, 3H, OMe), 13.06 (s, 1H, α-OH), 13.25 (s, 1H, α-OH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.4 (Me), 12.6 (Me), 61.9 (OMe), 107.5, 109.0, 127.3, 140.0, 141.1, 156.2, 165.9, 166.9, 173.3 (C=O), 174.0 (C=O). IR ($CHCl_3$): 2951, 1606 (C=O), 1577, 1448, 1408, 1393, 1285, 1265, 1200, 1182, 1155, 1043 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{11}O_5Cl$ 282.0295 found 282.0308.

2,3-Dichloro-5,8-dimethoxynaphthalene-1,4-dione (9a). Dichloronaphthazarine **7a** was methylated by CH_3I/Ag_2O according Brassard procedure[15] and yielded 2,3-dichloro-5,8-dimethoxynaphthalene-1,4-dione **(9a)**; red solid, mp: 236–237 °C, (lit. data[15], mp: 237–238 °C).

2,3,6,7-Tetrachloro-5,8-dimethoxynaphthalene-1,4-dione (9b).[18] A mixture of tetrachloronaphthazarine **7b** (6.72 g, 0.02 M), CH_3I (13 mL), and Ag_2O (10.0 g), was stirred at room temperature. The same amounts of CH_3I and Ag_2O were added after 6 and 16 h of the reaction, and the reaction mixture was stirred 29 h until complete conversion of red quinone **7b**, R_f 0.80 (A), into yellow dimethoxyquinone **9b**, R_f 0.75 (A). Inorganic salts were filtered off, the residue was washed with $CHCl_3$, combined filtrate was evaporated, and the residue was crystallized from $CHCl_3$ to give 2,3,6,7-tetrachloro-5,8-dimethoxynaphthalene-1,4-dione **(9b)**. Yield 5.60 g (80%), beige powder, mp: 208–210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 4.00 (6H, s, 2 × OMe). ^{13}C NMR (125 MHz, $CDCl_3$): 62.1 (2), 123.3 (2), 138.1 (2), 143.0 (2), 154.2 (2), 173.7 (2). IR ($CHCl_3$): 3014, 2981, 2856, 1687 (C=O), 1586, 1524, 1379, 1321, 1201, 1163, 1054, 1029 cm^{-1}. MS (EI, 70 eV), *m/z* (%): 356 (M^+, 100), 339 (42), 291 (42), 255 (36), 233 (59), 205 (27), 155 (21), 123 (21), 87 (87), 32 (83). HRMS (EI): calcd 353.9020 for $C_{12}H_6Cl_4O_4$, found 353.9034.

3-Chloro-2,5,8-trimethoxyaphthalene-1,4-dione (10a) and 2,6,7-trichloro-3,5,8-trimethoxynaphtalene-1,4-dione (10b). 2,3-Dichloroquinone **9a,b** (1.00 mM), dry AcONa 400 mg (2.40 mM) and dry methanol (30 mL) were stirred at reflux within 15 h for (**9a**) and 5 h for (**9b**). The hot reaction mixture was filtrated off from inorganic salts and then was cooled at +5 °C. Upon filtration methoxychloroquinones **10a,b** were obtained: 3-chloro-2,5,8-trimethoxyaphthalene-1,4-dione **(10a)**, yield 238 mg (85%), yellow needles, R_f 0.39 (A), mp 144–146 °C. (lit. data[19], mp 146–148 °C); 2,6,7-trichloro-3,5,8-trimethoxynaphtalene-1,4-dione **(10b)**, yield 263 mg (75%), yellow needles, R_f 0.41 (A), mp 156–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H, OMe), 3.99 (s, 3H, OMe), 4.25 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 61.5 (OMe), 62.0 (OMe), 62.2 (OMe), 123.4, 123.7, 127.2, 136.9, 137.6, 153.4, 153.5, 156.7, 176.2 (C=O), 177.4 (C=O). IR ($CHCl_3$): 2944, 1676 (C=O), 1603, 1525, 1459, 1380, 1331, 1307, 1117, 1029 cm^{-1}. HRMS (EI): calcd for $C_{13}H_9O_5Cl_3$ 349.9515 found 349.9532.

2,3-Diglucosides 11a,b. 2,3-Dichloronaphthoquinone **9a,b** (0.50 mM) was dissolved in acetone (20 mL) and MeOH (20 mL) and glucose sodium salt **6** 275 mg (1.26 mM) was added. The resulting mixture was stirred

during 1.5 h at room temperature until the conversion of starting quinone **9a,b** with R_f 0.90–0.95 (B) into a new yellow compound with R_f 0.27–0.28 (B). Inorganic salts were filtered off, and the precipitate was washed with acetone. The combined filtrate was evaporated in vacuum, and the residue was subjected to preparative TLC and led to 2,3-bisglucosides **11a,b**.

2,3-Di(β-D-glucopyranosyl-1-thio)-5,8-dimethoxynaphthalene-1,4-dione (11a). Yield 287 mg (94%), amorphous brown powder, R_f 0.27 (B), mp >360 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.00 (m, 2H, 2 × H-5'), 3.18 (m, 6H, 2 × H-2', 2 × H-3', 2 × H-4'), 3.42 (m, 4H, 4 × H-6'), 3.80 (s, 6H, 2 × OMe), 4.24 (br.s, 2H, 2 × $C^{6'}H_2O\underline{H}$), 4.93 (br.s, 2H, 2 × $C^{4'}HO\underline{H}$), 5.10 (br.s, 2H, 2 x $C^{3'}HO\underline{H}$), 5.12 (d, 2H, *J* 9.2 Hz, 2 × H-1'), 5.44 (br.s, 2H, 2 × $C^{2'}HO\underline{H}$), 7.41 (s, 2H, H-6, H-7). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 56.62 (MeO), 60.25 (C-6'), 69.30 (C-4'), 74.48 (C-2'), 78.16 (C-3'), 81.31 (C-5'), 83.59 (C-1'), 119.64, 122.16, 144.68, 151.93, 178.04 (C=O). IR (KBr): 3420 (OH), 2922, 1667 (C=O), 1592, 1568, 1525, 1481, 1435, 1414, 1278, 1257, 1211, 1181, 1050, 933 cm^{-1}.MS (ESI): *m/z* 629 [M+Na]. HRMS (ESI): calcd for $C_{24}H_{30}NaO_{14}S_2$ 629.0969, found 629.0971.

6,7-Dichloro-2,3-di(β-D-glucopyranosyl-1-thio)-5,8-dimethoxynaphthalene-1,4-dione (11b). Yield 301 mg (89%), brown solid, R_f 0.28 (B), mp 151–152 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.03 (m, 2H, 2 × H-5'), 3.15 (m, 6H, 2 × H-2', 2 × H-3', 2 × H-4'), 3.39 (m, 2H, 2 × H-6'), 3.48 (m, 2H, 2 × H-6'), 3.87 (s, 6H, 2 × OMe), 4.30 (br.s, 2H, 2 × $C^{6'}H_2O\underline{H}$), 4.94 (d, 2H, *J* 5.2 Hz, 2 × $C^{4'}HO\underline{H}$), 5.11 (br.s, 2H, 2 × $C^{3'}HO\underline{H}$), 5.15 (d, 2H, *J* 9.1 Hz, 2 × H-1'), 5.51 (br.s, 2H, *J* 5.5 Hz, 2 × $C^{2'}HO\underline{H}$). ^{13}C NMR (DMSO-d_6, 175 MHz): δ 60.5 (C-6'), 62.3 (MeO), 69.5 (C-4'), 74.8 (C-2'), 78.1 (C-3'), 81.6 (C-5'), 83.6 (C-1'), 126.3, 133.8, 145.4, 151.7, 176.5. IR (KBr): 3403 (OH), 2936, 1672 (C=O), 1521, 1459, 1382, 1317, 1195, 1166, 1046, 1023, 877, 808, cm^{-1}. MS (ESI): *m/z* 697 [M+Na]. HRMS (ESI): calcd for $C_{24}H_{28}Cl_2NaO_{14}S_2$ 697.0190, found 697.0181.

Tetracyclic quinones 12a,b. 2,3-Dichloronaphthoquinone **9a,b** (0.50 mM) was dissolved in mixture of acetone (20 mL) and MeOH (20 mL) and thioglucose sodium salt **6** 275 mg (1.26 mM) was added and stirred 15–20 min until complete conversion quinone **9a,b** in dithioglucoside **11a,b**. The reaction mixture was evaporated under reduced pressure to remove acetone. The residue was dissolved in MeOH (15 mL) and 0.5 N MeONa/MeOH (0.6 mL, 0.3 mM) was added. The mixture was kept at room temperature until TLC analysis indicated complete consumption of **11a,b** (after 1 h) and formation new compound **12a,b**. During the reaction of **9a**, the formation of a brown precipitate **12a** was observed. The precipitate was filtered of, washed with water, dry MeOH and gave high purity quinone **12a**. The reaction mixture with quinone **12b** was concentrated further and subjected preparative TLC; double development with system B gave orange band of quinone **12b**. The quinone **12b** was eluted from SiO_2 with acetone and equal volume of MeOH was added to acetone eluate. Gently evaporation of this solution on reduced pressure led to formation pure orange solid of tetracyclic quinone **12b**.

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Hydroxymethyl-3,4,-dihydroxy-7,10-dimethoxy-3,4,4a,12a-tetrahydro-2*H*-naphtho-[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (12a). Yield 176 mg (86%), red solid, R_f 0.50 (C), mp 332–335 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.29 (m, 1H, H-3), 3.48 (m, 3H, H-2, H-4a, H-13) 3.57 (m, 1H, H-4), 3.74 (m, 1H, H-13), 3.85 (s, 3H, ArOMe), 3.86 (s, 3H, ArOMe), 4.72 (br.s, 1H, $C^{13}H_2O\underline{H}$), 4.92 (d, 1H, *J* 8.5 Hz, H-12a), 5.37 (br.s, 1H, $C^3HO\underline{H}$), 5.58 (br.s, 1H, $C^4HO\underline{H}$), 7.52 (d, 1H, *J* 9.7 Hz, ArH), 7.54 (d, 1H, *J* 9.7 Hz, ArH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 56.7 (OMe), 56.8 (OMe), 60.8 (C-13), 70.5 (C-3), 73.7 (C-12a), 73.9 (C-4), 79.2 (C-4a), 82.2 (C-2), 118.6, 118.9, 121.7, 122.0, 122.4, 149.7, 153.3, 153.8, 174.7 (C=O), 179.9 (C=O). IR (KBr) 3444 (OH), 1638 (C=O), 1614, 1561, 1476, 1405, 1266, 1181, 1075, 935 cm^{-1}. MS (ESI): *m/z* 433 [M+Na]. HRMS (ESI): calcd for $C_{18}H_{18}NaO_9S$ 433.0564, found 433.0562.

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-8,9-Dichloro-2-hydroxymethyl-3,4-dihydroxy-7,10-dimethoxy-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (12b). Yield 198 mg (83%), orange solid, R_f 0.28 (C), mp 222–224 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.32 (m, 1H, H-3), 3.50 (m, 2H, H-2, H-13,) 3.54 (m, 1H, H-

4a), 3.60 (m, 1H, H-4), 3.75 (m, 1H, H-13), 3.82 (s, 3H, ArOMe), 3.83 (s, 3H, ArOMe), 4.74 (m, 1H, $C^{13}H_2O\underline{H}$), 4.96 (d, 1H, *J* 8.0 Hz, H-12a), 5.40 (d, 1H, *J* 5.9 Hz, $C^3HO\underline{H}$), 5.67 (d, 1H, *J* 5.9 Hz, $C^4HO\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 60.7 (C-13), 61.5 (2OMe), 70.4 (C-3), 73.6 (C-12a), 73.9 (C-4), 79.3 (C-4a), 82.2 (C-2), 123.1, 123.4, 123.9, 135.1, 135.3, 149.9, 152.3, 152.9, 173.4 (C=O), 178.9 (C=O). IR (KBr): 3432, 2941, 1653, 1603, 1625, 1458, 1381, 1333, 1275, 1209, 1131, 1025, 951 cm^{-1}. MS (ESI): *m/z* 500 [M+Na]. HRMS (ESI): calcd for $C_{18}H_{16}Cl_2NaO_9S$ 500.9784, found 500.9784.

Acetylation of tetracycles 12a,b by Ac_2O/Py. Quinone **12a,b** (0.20 mM) was dissolved in Py (3.0 mL), Ac_2O (1.5 mL) was added and stand overnight at room temperature. The reaction mixture was poured into ice, the precipitate was triturated with ice before crystals formation. The crystals were filtered off, washed with diluted HCl, water, dried, recrystallized from MeOH-benzene to give:

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Acetoxymethyl-3,4,-diacetoxy-7,10-dimethoxy-3,4,4a,12a-tetrahydro-2*H*-naphtho-[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (13a). Yield 91 mg (85%), orange solid, mp 235–237 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 2.02 (s, 3H, AcO), 2.04 (s, 3H, AcO), 2.08 (s, 3H, AcO), 3.85 (s, 3H, ArOMe), 3.86 (s, 3H, ArOMe), 3.99 (dd, 1H, *J* 8.4, 9.6 Hz, H-4a), 4.10 (dd, 1H, *J* 2.2, 12.6 Hz, H-13), 4.18 (dd, 1H, *J* 5.5, 12.6 Hz, H-13), 4.23 (ddd, 1H, *J* 2.2, 5.5, 9.6 Hz, H-2), 5.07 (dd, 1H, *J* 9.6 Hz, H-3), 5.28 (d, 1H, *J* 8.4 Hz, H-12a), 5.53 (dd, 1H, *J* 9.6 Hz, H-4), 7.54 (d, 1H, *J* 9.5 Hz, ArH), 7.56 (d, 1H, *J* 9.5 Hz, ArH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 20.4 ($C\underline{H}_3CO$), 20.5 ($C\underline{H}_3CO$), 20.6 ($C\underline{H}_3CO$), 56.67 (OMe), 56.70 (OMe), 61.8 (C-13), 68.3 (C-3), 71.7 (C-4), 73.2 (C-12a), 75.5 (C-5), 75.7 (C-2), 118.3, 118.6, 121.8, 122.0, 122.5, 148.6, 153.4, 153.9, 169.3 ($CH_3\underline{C}O$), 169.4 ($CH_3\underline{C}O$), 170.1 ($CH_3\underline{C}O$), 174.1 (C=O), 179.6 (C=O). IR ($CHCl_3$): 2941, 1753 (CH_3COOR), 1664 (C=O), 1651, 1613, 1567, 1478, 1463, 1435, 1408, 1370, 1341, 1267, 1098, 1065, 1031 cm^{-1}. HRMS (ESI, *m/z*): $[M-H]^-$ calcd 535.0916 for $C_{24}H_{24}O_{12}S$ found 535.0908, and

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Acetoxymethyl-3,4,-diacetoxy-8,9-dichloro-7,10-dimethoxy-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (13b). Yield 102 mg (84%), orange solid, mp 159–162 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 2.07 (s, 3H, AcO), 2.11 (s, 3H, AcO), 2.16 (s, 3H, AcO), 3.88 (dd, 1H, *J* 8.4, 9.7 Hz, H-4a), 3.93 (ddd, 1H, *J* 2.2, 4.9, 9.5 Hz, H-2), 3.94 (s, 6H, ArOMe), 4.20 (dd, 1H, *J* 2.2, 12.6 Hz, H-13), 4.30 (dd, 1H, *J* 4.9, 12.6 Hz, H-13), 4.84 (d, 1H, *J* 8.4 Hz, H-12a), 5.22 (dd, 1H, *J* 9.7, 9.8 Hz, H-3), 5.45 (dd, 1H, *J* 9.5, 9.7 Hz, H-4). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 20.6 ($C\underline{H}_3CO$), 20.7 (2 × $C\underline{H}_3CO$), 61.7 (C-13), 61.9 (OMe), 62.0 (OMe), 68.3 (C-3), 72.2 (C-4), 74.6 (C-12a), 76.5 (C4a), 77.2 (C-2), 122.8, 123.4, 124.6, 137.3, 137.5, 149.0, 153.5, 154.0, 169.4 ($CH_3\underline{C}O$), 170.0 ($CH_3\underline{C}O$), 170.5($CH_3\underline{C}O$), 173.0 (C=O),178.8 (C=O). IR ($CHCl_3$): 2943, 1754 (CH_3CO_2R), 1672(C=O), 1658, 1601, 1526, 1458, 1380, 1329, 1146, 1102, 1067, 1029 cm^{-1}. HRMS (ESI, *m/z*): $[M-H]^-$ calcd 603.0136 for $C_{24}H_{22}Cl_2O_{12}S$ found 603.0137.

3-(β-D-Glucopyranosyl-1-thio)-2,5,8-trimethoxynaphthalene-1,4-dione (14a). Quinone **10a** 141 mg (0.50 mM) was dissolved in acetone (10 mL) and MeOH (10 mL), thioglucose sodium salt **6** 110 mg (0.50 mM) was added. The resulting mixture was stirred during 0.6 h at room temperature until the consumption of thioglucose **6** and conversion of the starting quinone **10a** in the new orange compound with R_f 0.45 (B). Inorganic salts were filtered off, the precipitate was washed with acetone. The combined filtrate was evaporated in vacuum, the residue was subjected to preparative TLC (system B) and yielded 3-(β-D-glucopyranosyl-1-thio)-2,5,8-trimethoxynaphthalene-1,4-dione **(14a)**; yield 177 mg (80%), brown solid, mp 129–131 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.02 (m, 1H, H-5'), 3.07 (m, 1H, H-2'), 3.16 (m, 1H, H-4'), 3.20 (m, 1H, H-3'), 3.42 (m, 2H, 2 × H-6'), 3.81 (s, 3H, ArOMe), 3.85 (s, 3H, ArOMe), 3.95 (s, 3H, ArOMe), 4.27 (m, 1H, $C^{6'}H_2O\underline{H}$), 4.88 (d, 1H, *J* 4.5 Hz, $C^{4'}HO\underline{H}$), 5.08 (m, 1H, $C^{3'}HO\underline{H}$), 5.18 (d, 1H, *J* 9.6 Hz, H-1'), 5.43 (d, 1H, *J* 5.6 Hz, $C^{2'}HO\underline{H}$), 7.45 (d, 1H, *J* 9.5 Hz, ArH), 7.48 (d, 1H, *J* 9.5 Hz, ArH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 56.6 (MeO), 56.8 (MeO), 60.2 (MeO), 60.4 (C-6'), 69.6 (C-4'), 74.3 (C-2'), 78.2 (C-3'), 81.1 (C-5'), 82.0 (C-1'), 119.7, 120.3, 121.0, 121.5, 130.2, 152.2, 152.9, 156.2, 177.1 (C=O), 181.3 (C=O). IR (KBr): 3444 (OH), 2938, 1645 (C=O),

1595, 1565, 1478, 1434, 1410, 1340, 1274, 1206, 1053, 1017, 917 cm^{-1}. MS (ESI): *m/z* 465 [M+Na]. HRMS (ESI): calcd for $C_{19}H_{22}NaO_{10}S$ 465.0826, found 465.0821.

6,7-Dichloro-3-(β-D-glucopyranosyl-1-thio)-2,5,8-trimethoxynaphthalene-1,4-dione (14b). Quinone **10b** 176 mg (0.50 mM) was dissolved in acetone (10 mL) and MeOH (10 mL) and thioglucose sodium salt **6** 110 mg (0.50 mM) was added. The resulting mixture was stirred during 1.0 h at room temperature until the consumption of thioglucose **6** and formation of two new orange compounds with R_f 0,46 (B) and R_f 0.49 (B). The reaction mixture was evaporated under reduced pressure. The residue was subjected preparative TLC (system B) and led to tetracyclic quinone **12b**, R_f 0.49 (B) 17 mg (7%), and 6,7-dichloro-3-(β-D-glucopyranosyl-1-thio)-2,5,8-trimethoxynaphthalene-1,4-dione **(14b)**; yield 189 mg (74 %), brown solid, R_f 0.46 B), mp 103–105 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.03 (m, 1H, H-5'), 3.09 (m, 2H, H-2', H-4'), 3.21 (m, 1H, H-3'), 3.37 (m, 1H, H-6'), 3.49 (m, 1H, H-6'), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.02 (s, 3H, OMe), 4.30 (m, 1H, $C^{6'}H_2O\underline{H}$), 4.92 (d, 1H, *J* 5.2 Hz, $C^{4'}HO\underline{H}$), 5.11 (m, 1H, $C^{3'}HO\underline{H}$), 5.21 (d, 1H, *J* 9.8 Hz, H-1'), 5.48 (d, 1H, *J* 6.4 Hz, $C^{2'}HO\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 60.6 (MeO), 60.7 (C-6'), 61.8 (MeO), 62.1 (MeO), 69.8 (C-4'), 74.4 (C-2'), 78.1 (C-3'), 81.3 (C-5'), 82.2 (C-1'), 124.6, 125.6, 130.2, 134.2, 134.3, 151.8, 152.0, 157.0, 175.9 (C=O), 179.9 (C=O). IR (KBr): 3430 (OH), 2939, 1715, 1662 (C=O), 1583, 1546, 1459, 1381, 1326, 1273, 1180, 1117, 1026 cm^{-1}. MS (ESI): *m/z* 533 [M+Na]. HRMS (ESI): calcd for $C_{19}H_{20}Cl_2NaO_{10}S$ 533.0046, found 533.0046.

2-Chloro-3-(β-D-glucopyranosyl-1-thio)-5,8-dihydroxynaphthalene-1,4-dione (15a) and 2,3-di(β-D-glucopyranosyl-1-thio)-5,8-dihydroxynaphthalene-1,4-dione (15b). 2,3-Dichloroquinone **7a** 130 mg (0.50 mM) was dissolved in acetone (10 mL) and MeOH (10 mL) and thioglucose sodium salt **6** 194 mg (0.91 mM) was added. The resulting mixture was stirred during 1.0 h at room temperature until the consumption of thioglucose **6** and formation of two new red compounds with R_f 0.55 (B) and R_f 0.20 (B). The reaction mixture was evaporated under reduced pressure. The residue was subjected preparative TLC (system B) and yielded 2-chloro-3-(β-D-glucopyranosyl-1-thio)-5,8-dihydroxynaphthalene-1,4-dione **(15a)**; yield 44 mg (21 %), dark red solid, mp 154-157 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.10 (t, 1H, H-3'), 3.11 (m, 1H, H-5'), 3.15 (t, 1H, *J* 9.2 Hz, H-5'), 3.23 (t, 1H, *J* 8.3 Hz, H-4'), 3.31 (dd, 1H, *J* 5.7, 12 Hz, H-6), 3.46 (dd, 1H, *J* 1.9, 12 Hz, H-6'), 4.25 (br.s, 2H, 2 × OH), 4.94 (br.s, 2H, 2 × OH), 5.55 (d, 1H, *J* 9.7 Hz, H-1'), 7.39 (s, 2H, 2 × ArH), 11.84 (s, 1H, α-OH), 12.01 (s, 1H, α-OH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 60.7 (C-6'), 70.0 (C-4'), 74.9 (C-2'), 78.2 (C-3'), 81.7 (C-5'), 83.7 (C-1'), 111.4, 112.2, 129.2, 129.4, 140.6, 147.9, 156.9, 157.1, 177.9 (C=O), 181.9 (C=O). IR (KBr): 3368 (OH), 2919, 1711, 1617 (C=O), 1574, 1535, 1450, 1403, 1358, 1309, 1265, 1226, 1201, 1088, 1050, 988, 880, 780 cm^{-1}. MS (ESI): *m/z* 441 [M+Na]. HRMS (ESI): calcd for $C_{16}H_{15}ClNaO_9S$ 441.0018, found 441.0017 and 2,3-di(β-D-glucopyranosyl-1-thio)-5,8-dihydroxynaphthalene-1,4-dione **(15b)**. Yield 199 mg (69%), red solid. mp 179–181 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.09 (m, 4H, 2 × H-4', 2 × H-5'), 3.16 (dd, 2H, *J* 8.5, 9.7 Hz, 2 × H-2'), 3.20 (dd, 2H, *J* 8.2, 8.5 Hz, 2 × H-3'), 3.32 (dd, 2H, *J* 5.0, 12.0 Hz, 2 × H-6'), 3.48 (d, 2H, *J* 12.0 Hz, 2 × H-6'), 4.28 (br.s, 2H, 2 × $C^{6'}H_2O\underline{H}$), 4.95 (br.s, 4H, 2 × $C^{3'}HO\underline{H}$, 2 × $C^{4'}HO\underline{H}$), 5.40 (d, 2H, *J* 8.4 Hz, 2 × H-1'), 5.52 (br.s, 2H, 2 × $C^{2'}HO\underline{H}$), 7.33 (s, 2H, H-6, H-7), 12.06 (s, 2H, 2 × α-OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 60.8 (C-6'), 70.0 (C-4'), 75.0 (C-2'), 78.2 (C-3'), 81.6 (C-5'), 84.0 (C-1'), 112.1, 128.6, 147.3, 156.4, 181.9 (C=O). IR (KBr): 3421 (OH), 2922, 2360, 1615 (C=O), 1456, 1403, 1485, 1361, 1235, 1200, 1164, 1075, 1039 cm^{-1}. MS (ESI): *m/z* 601 [M+Na]. HRMS (ESI): calcd for $C_{22}H_{26}NaO_{14}S_2$ 601.0656, found 601.0658.

2,3-Di(β-D-glucopyranosyl-1-thio)-5,8-dihydroxy-6,7-dimethylnaphthalene-1,4-dione (15c). 2,3-Dichloroquinone **7b** 144 mg (0.50 mM) was dissolved in acetone (10 mL) and MeOH (10 mL) and thioglucose sodium salt **6** 275 mg (1.26 mM) was added. The resulting mixture was stirred during 18 h at room temperature until the consumption of quinone **7b** and formation of the new red compound with R_f 0.23 (B). The reaction mixture was evaporated under reduced pressure. The residue was subjected preparative TLC (system B) and yielded 2,3-di(β-D-glucopyranosyl-1-thio)-5,8-dihydroxy-6,7-dimethylnaphthalene-1,4-dione **(15c)**; yield 288 mg (95%), red solid, mp 198–200 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 2.22 (s, 6H, 2 × $ArCH_3$),

3.05 (ddd, 2H, *J* 1.8, 5.6, 9.6 Hz, 2 × H-5'), 3.10 (dd, 2H, *J* 8.8, 9.5 Hz, 2 × H-4'), 3.15 (dd, 2H, *J* 8.8, 9.6 Hz, 2 × H-2'), 3.21 (dd, 2H, *J* 8.6 Hz, 2 × H-3'), 3.33 (dd, 2H, *J* 5.6, 12.0 Hz, 2 × H-6'), 3.45 (dd, 2H, *J* 1.8, 12.0 Hz, 2 × H-6'), 4.30 (br.s, 2H, 2 × $C^{6'}H_2O\underline{H}$), 4.99 (br.s, 2H, 2 × $C^{4'}HO\underline{H}$), 5.15 (br.s, 2H, 2 × $C^{3'}HO\underline{H}$), 5.41 (d, 2H, *J* 9.6 Hz, 2 × H-1'), 5.51 (br.s, 2H, 2 × $C^{2'}HO\underline{H}$),), 13.09 (s, 2H, 2 × α-OH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 12.28, ($ArCH_3$), 60.7 (C-6'), 69.9 (C-4'), 75.0 (C-2'), 78.2 (C-3'), 81.5 (C-5'), 84.0 (C-1'), 109.0, 138.1, 145.8, 160.6, 178.2 (C=O). IR (KBr): 3409 (OH), 2890, 1600 (C=O), 1447, 1400, 1360, 1268, 1213, 1096, 1076, 1050, 878, 809 cm^{-1}. MS (ESI): *m/z* 629 [M+Na]. HRMS (ESI): calcd for $C_{24}H_{30}NaO_{14}S_2$ 629.0969, found 629.0956.

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Hydroxymethyl-3,4,7,10-tetrahydroxy-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]-pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (16a). Dithioglucoside **15b** 87 mg (0.15mM) was dissolved in MeOH (30 mL) and 0.5 N solution of MeONa/MeOH (1.4 mL, 0.70 mM) was added. The reaction mixture changed color from red to dark blue and the dark blue precipitate of bisthiogluside **15b** sodium salt was formed. The reaction mixture was stirred at room temperature during 21 h, until consumption of bisthiogluside **15b**, acidified by dropwise addition of conc. HCl and was evaporated under reduced pressure. The residue was subjected preparative TLC (system C). The main red band with R_f 0.43 was eluted from SiO_2 with acetone. The acetone eluate was dissolved by equal volume of MeOH and the solution was gently evaporated on reduced pressure and led (2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-hydroxymethyl-3,4,7,10-tetrahydroxy-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione **(16a)**; yield 10 mg (17%), red solid, mp 312–315 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.33 (m, 1H, H-3), 3.50 (m, 1H, H-2), 3.51 (m, 1H, H-13), 3.61 (m, 2H, H4, H-4a), 3.75 (m, 1H, H-13), 4.74 (m, 1H, $C^{13}H_2O\underline{H}$), 5.03 (m, 1H, H-12a), 5.43 (d, 1H, *J* 5.8 Hz, $C^3HO\underline{H}$), 5.70 (m, 1H, $C^4HO\underline{H}$), 7.34 (d, 1H, *J* 9.3 Hz, ArH), 7.36 (d, 1H, *J* 9.3 Hz, ArH), 11.88 (s, 1H, α-OH), 12.15. (s, 1H, α-OH). ^{13}C NMR (DMSO-d_6, 176 MHz): δ 60.7 (C-13), 70.4 (C-3), 73.4 (C-12a), 73.8 (C-4), 79.3 (C-4a), 82.3 (C-2), 110.4, 110.5, 124.0, 129.3 (2 × ArH), 150.6, 155.8, 156.7, 178.9 (C=O), 184.3 (C=O). IR (KBr): 3402 (OH), 2923, 1601 (C=O), 1579, 1448, 1413, 1241, 1223, 1182, 1142, 1077, 979 cm^{-1}. MS (ESI): *m/z* 405 [M+Na]. HRMS (ESI): calcd for $C_{16}H_{14}NaO_9S$ 405.0251, found 405.0255.

(2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-Hydroxymethyl-3,4,7,10-tetrahydroxy-8,9-dimethyl-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione (16b). Dithioglucoside **15c** 91 mg (0.15 mM) was dissolved in MeOH (30 mL) and 0.5 N solution of MeONa/MeOH (1.4 mL, 0.70 mM) was added with formation of dark blue suspension of bisthioglucoside **15c** sodium salt. The reaction mixture changed color from red to dark blue and the dark blue solution was formed. The reaction mixture was stirred at room temperature during 6 h, until consumption of bisthioglucoside **15c**, acidified by dropwise addition of conc. HCl and was evaporated under reduced pressure. The residue was subjected preparative TLC (system C). The main red band with R_f 0.47 was eluted from SiO_2 with acetone. The acetone eluate was dissolved by equal volume of MeOH and the solution was gently evaporated on reduced pressure and led the sample (2*R*,3*R*,4*S*,4a*R*,12a*S*)-2-hydroxymethyl-3,4,7,10-tetrahydroxy-8,9-dimethyl-3,4,4a,12a-tetrahydro-2*H*-naphtho[2,3-*b*]pyrano[2,3-*e*][1,4]-oxathiine-6,11-dione **(16b)**; yield 53 mg (85%), red solid, mp 315–318 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 3H, ArMe), 2.19 (s, 3H, ArMe), 3.32 (m, 1H, H-3), 3.50 (m, 2H, H-2, H-13), 3.60 (m, 2H, H-4, H-4a), 3.75 (m, 1H, H-13), 4.81 (m, 1H, $C^{13}H_2O\underline{H}$), 5.01 (m, 1H, H-12a), 5.49 (d, 1H, *J* 5.9 Hz, $C^3HO\underline{H}$), 5.76 (m, 1H, $C^4HO\underline{H}$), 12.64 (s, 1H, α-OH), 12.94. (s, 1H, α-OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.1 (Me), 12.2 (Me), 60.7 (C-13), 70.4 (C-3), 73.4 (C-12a), 73.9 (C-4), 79.3 (C-4a), 82.3 (C-2), 117.3, 107.4, 123.5, 137.8, 137.9, 150.4, 156.3, 157.3, 177.7 (C=O), 183.0 (C=O). IR (KBr): 3416 (OH), 2925, 1595 (C=O), 1570, 1448, 1387, 1307, 1266, 1181, 1089, 1076, 1038, 979, 809 cm^{-1}. MS (ESI): *m/z* 433 [M+Na]. HRMS (ESI): calcd for $C_{18}H_{18}NaO_9S$ 433.0564, found 433.0554.

2-(β-D-Glucopyranosyl-1-thio)-5,8-dihydroxy-3-methoxynaphthalene-1,4-dione (17a). Quinone **8a** 113 mg (0.40 mM) was dissolved in acetone (10 mL) and MeOH (10 mL), thioglucose sodium salt **6** 110 mg (0.50 mM) was added. The resulting mixture was stirred during 1.5 h at room temperature until the consumption of

thioglucose **6** and conversion of the starting quinone **8a** in two new red compounds with R_f 0.45 (B) and R_f 0.20 (B). The resulting mixture was evaporated in vacuum and residue was subjected preparative TLC and gave 2-(β-D-glucopyranosyl-1-thio)-5,8-dihydroxy-3-methoxynaphthalene-1,4-dione **(17a)**; yield 132 mg (80%), red solid, R_f 0.45 (B), mp 192–194 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.09 (m, 3H, H-2', H-4', H-5'), 3.22 (m, 1H, H-3'), 3.35 (m, 1H, H-6'), 3.56 (m, 1H, H-6'), 4.15 (s, 1H, OMe), 4.37 (t, 1H, *J* 5.9 Hz, C$^{6'}$H$_2$OH), 4.95 (d, 1H, *J* 5.4 Hz, C$^{4'}$HOH), 5.11 (d, 1H, *J* 5.0 Hz, C$^{3'}$HOH), 5.27 (d, 1H, *J* 10.0 Hz, H-1'), 5.48 (m, 1H, *J* 6.5 Hz, C$^{2'}$HOH), 7.35 (s, 2H, 2 × Ar-H), 12.02 (s, 1H, α-OH), 12.21 (s, 1H, α-OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 61.0 (C-6'), 61.5 (MeO), 70.0 (C-4'), 74.5 (C-2'), 78.1 (C-3'), 81.4 (C-5'), 82.7 (C-1'), 111.3, 111.7, 128.8, 129.2, 131.5, 156.0, 156.5, 158.4, 181.5 (C=O), 186.1 (C=O). IR (KBr): 3420 (OH), 2948, 2886, 1608 (C=O), 1557, 1455, 1407, 1263, 1192, 1135, 1263, 1192, 1135, 1079, 1063, 1035, 980 cm^{-1}. MS (ESI): *m/z* 465 [M+Na]. HRMS (ESI): calcd for $C_{17}H_{18}NaO_{10}S$ 437.0513, found 437.0512 and known dithioglucoside **15a** 35 mg (15%).

2-(β-D-Glucopyranosyl-1-thio)-5,8-dihydroxy-3-methoxy-6,7-dimethylnaphthalene-1,4-dione (17b). Quinone **8b** 99 mg (0.35 mM) was dissolved in acetone (10 mL) and MeOH (10 mL), thioglucose sodium salt **6** 110 mg (0.45 mM) was added. The resulting mixture was stirred during 1.5 h at room temperature until the consumption of thioglucose **6** was observed. The starting quinone **8b** was converted in three new red compounds with R_f 0.47 (B), R_f 0.40 (B) and R_f 0.10 (B). The reaction mixture was evaporated in vacuum and residue was subjected preparative TLC and gave tetracyclic quinone **16b**, R_f 0.47 (B), yield 8 mg (5.5%), 2-(β-D-glucopyranosyl-1-thio)-5,8-dihydroxy-3-methoxy-6,7-dimethylnaphthalene-1,4-dione **(17b)**, R_f 0.40 (B), yield 130 mg (84%), red solid, mp 195–196 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (s, 6H, 2 × OMe), 3.09 (m, 3H, H-2', H-4', H-5'), 3.23 (m, 1H, H-3'), 3.35 (dd, 1H, *J* 5.5, 12.0 Hz, H-6'), 3.55 (dd, 1H, *J* 1.7, 12.0 Hz, H-6'), 4.13 (s, 1H, OMe), 4.35 (br.s, 1H, C$^{6'}$H$_2$OH), 4.97 (br.s, 2H, C$^{3'}$HOH, C$^{4'}$HOH), 5.27 (d, 1H, *J* 9.8 Hz, H-1'), 5.45 (br.s, 1H, C$^{2'}$HOH), 12.90 (s, 1H, α-OH), 13.13 (s, 1H, α-OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.1 (Me), 12.3 (Me), 61.0 (C-6'), 61.4 (MeO), 70.0 (C-4'), 74.5 (C-2'), 78.1 (C-3'), 81.4 (C-5'), 82.9 (C-1'), 108.0, 109.0, 130.7, 138.0, 138.6, 158.0, 159.8, 160.4, 177.3 (C=O), 182.1 (C=O). IR (KBr): 3408 (OH), 2924, 1737, 1601 (C=O), 1555, 1444, 1387, 1260, 1181, 1141, 1098, 1075, 1034, 808 cm^{-1}. MS (ESI): *m/z* 465 [M+Na]. HRMS (ESI): calcd for $C_{19}H_{22}NaO_{10}S$ 465.0826, found 465.0821, and dithioglucoside **15c**, yield 11 mg (5%).

Preparation of tetracyclic quinones 16a,b from 3-methoxy-2-thioglucosides 17a,b. Thioglucoside **17a,b** (0.19 mM) was dissolved in MeOH (30 mL) and 0.5 N solution of MeONa/MeOH (1.5 mL, 0.75 mM) was added and the dark blue solution was formed. The reaction mixture was stirred at room temperature during 6 h for **17a** and 2.5 h for **17b** until conversion of starting quinones in tetracycles **16a,b**. The reaction mixture was acidified by dropwise addition of conc. HCl and was evaporated under reduced pressure. The residue was subjected preparative TLC (system C). The main red band was eluted from SiO_2 with acetone, the eluate was diluted with equal volume of MeOH and gently evaporated on reduced pressure and led to **16a**, R_f 0.43 (B), yield 65 mg (90%) and **16b**, R_f 0.47 (B), yield 71 mg (91%).

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Supplementary Material

^{1}H and ^{13}C NMR spectra are provided for all new compounds: **4a,b**; **8b**; **10b**; **11a,b**; **12a,b**; **13a,b**; **14a,b**; **15a,b**; **16a,b** and **17a,b**.

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