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Synthesis and antiproliferative activity of sulfa-Michael adducts and thiochromenes derived from carbohydrates

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Michael addition reactions of carbohydrate-derived nitroalkenes with ethyl thioglycolate and 2-mercaptobenzyl alcohol have been studied. Processes occurred under mild, solventless conditions, and with DABCO as catalyst, thus leading to the corresponding adducts in good yields. Furthermore, those compounds arising from 2-mercaptobenzyl alcohol have been used as starting materials for the preparation of chiral 3-nitro-2*H*-thiochromenes. For some compounds prepared herein, the antioxidant and antiproliferative activities against a panel of human solid tumor cell lines were assayed and compared with starting carbohydrate-nitroalkenes.

Introduction

The chemistry of thiopyrans has been much less explored than that of their pyran analogues; however, there is currently an increasing interest towards the synthesis of heterocycles containing sulfur such as thiochromanes and 2*H*-thiochromenes. For these compounds,[1] a wide range of biological activities has been identified and used in research and development of new pharmaceutical products.[2] Moreover, preparation of new 2*H*-thiochromenes is an active area of research[3] because of the recent finding of their anticancer activity.[4] Although there have been different methods describing the preparation of thiochromanes or thiochromenes,[1] their asymmetric synthesis either by using optically pure starting materials[5] or chiral auxiliaries[6] are rather scarce. In most cases, the initial step in the mechanism of their formation is a conjugate addition of thiols to electron-deficient olefins or a sulfa-Michael addition,[6f-h] and the second process is a nitroaldol reaction.[7] This way to generate carbon-sulfur bonds has found many applications in chemistry and biology,[8] being one of the most valuable synthetic methods for preparing optically active chiral thiocompounds which are widely used in organic and medicinal chemistry.[9] Thioglycolic acid has been used in asymmetric additions to (*E*)-*β*-nitrostyrene in the presence of cinchona alkaloids,[10] this being the first example on the use of chiral catalysts in these reactions. As they are relatively inexpensive and less toxic than other thiols,[11,12] thioglycolates are considered as a good source of sulfur for sulfa-Michael additions. Moreover, catalyzed additions of thiols to nitroalkenes were carried out under solventless conditions with tetrabutylammoniun bromide,[12] as well as cupreine catalyzed additions of 2-mercaptobenzaldehyde to (*E*)-*β*-nitrostyrene yielding functionalized chiral thiochromanes.[6i] In similar processes leading to chiral thiochromanes, amino-thiourea catalysts derived from cinchone were used.[13] Furthermore, addition reactions of thioacetic acid[14] and thiols[15] to alkyl- or aryl-nitroalkenes catalyzed by chiral thioureas, as well as the addition of thioacetic acid on *α*,*β*-disubstituted nitroalkenes with chiral catalysts derived from hexamethylendiamine have also been reported.[15c]

To the best of our knowledge, there are not previous examples[6d] on the syntheses of chiral thiochromanes and 2*H*-thiochromenes involving the addition of thiols to carbohydrate-derived nitroalkenes. Thus, the few heterocycles of these types bearing sugar side-chains as substituents[16] were obtained by other methods, or through interconversions between them. The only precedent found about the sulfa-Michael addition in the carbohydrate field[17] refers to the reaction of the sodium salt of 1-thio-D-glucose with 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-D-*arabino*-hex-1-enitol, the product being a 2.3:1.0 mixture of the corresponding diastereoisomeric adducts, and the major one showing to have a relative 2,3-*erythro* configuration.

This research provides results in previous QSAR studies because theoretical calculations about anticoccidial activity of *trans*-2-(2-nitrovinyl)furan[18] predicts that more than 50% of mentioned activity is due to *trans*-nitro-double bond system. Moreover, different research groups[19] have calculated the global electrophilicity index ω for cyclic carbohydrate-derived nitroalkenes and chromenes, finding that, when ω > 0.5, these compounds are more active as antiviral agents than when ω < 0.5. Antiproliferative activity of structurally related compounds obtained by our group[20] supports this hypothesis. This work aims to complete our previous study with the synthesis of thiochromenes.

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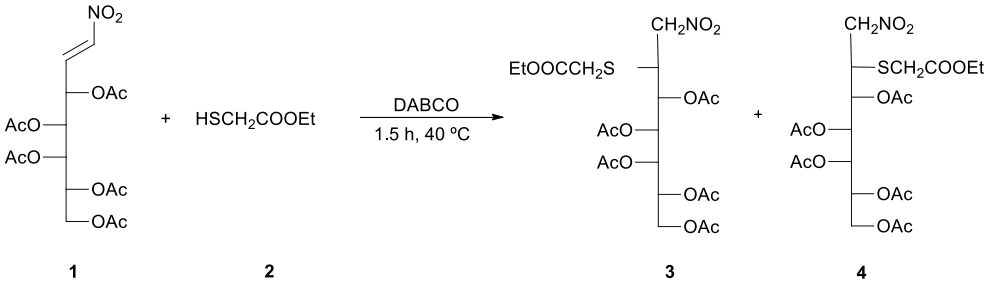


1 2 3 4

Scheme 1. Sulfa-Michael addition between compounds **1** and **2**

Herein we report the Michael addition reactions between thiols and carbohydrate-derived nitroalkenes. The adducts arising from 2-mercaptobenzyl alcohol have been used as starting materials to prepare chiral 3-nitro-2*H*-thiochromenes. Furthermore, several in vitro biological activities of some of the new compounds are described and compared to previous studies.

Results and Discussion

Sulfa-Michael addition reaction between ethyl thioglycolate 2 and (*E*)-3,4,5,6,7-penta-*O*-acetyl-1-nitro-D-*galacto*-nitrohept-1-enitol 1

The reaction between nitroalkene **1** and ethyl thioglycolate **2** was tested with and without solvents, as well as under different nitroalkene:DABCO ratios, being the best conditions those described in Experimental Section. The product was a 0.8:1.0 mixture of the Michael adducts **3** and **4** (Scheme 1), from which both were obtained pure by fractional crystallization.

Absolute C-2(*S*) configuration in **4** was unambiguously confirmed by X-ray crystallographic structure analysis[21] (Figure 1).

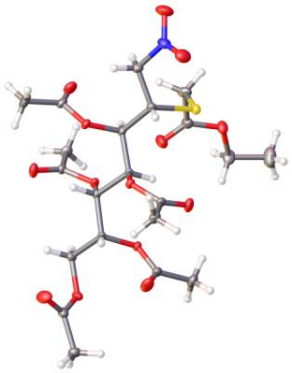


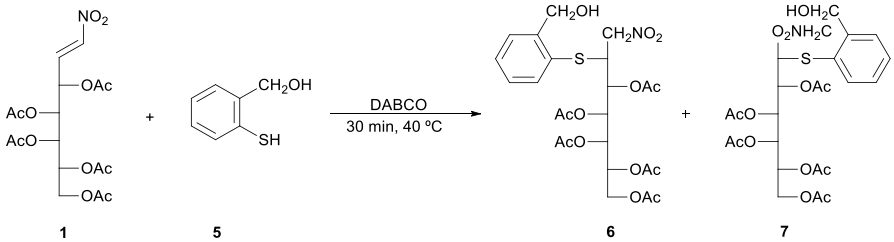
Figure 1. Solid-state structure of **4**. Thermal ellipsoids drawn at 50% probability level

Reaction between (*E*)-3,4,5,6,7-penta-*O*-acetyl-1-nitro-D-*galacto*-nitrohept-1-enitol 1 with 2-mercaptobenzyl alcohol 5

2-Mercaptobenzyl alcohol **5** was easily prepared with high yield by lithium alumnium hydride reduction from commercial 2-mercaptobenzoic acid. The sulfa-Michael addition between nitroalkene **1** and alcohol **5** was carried out for 30 min, under solventless conditions, in presence of DABCO as catalyst. The product was a 0.7:1.0 mixture of the Michael adducts **6** and **7** (Scheme 2), which could not been isolated by fractional crystallization from methanol. Absolute configuration at C-2 was assigned according to the preferential nucleophilic attack by the sulfur atom of **2** on the less-hindered face of nitroalkene **1** in its presumably most stable conformer.[22]

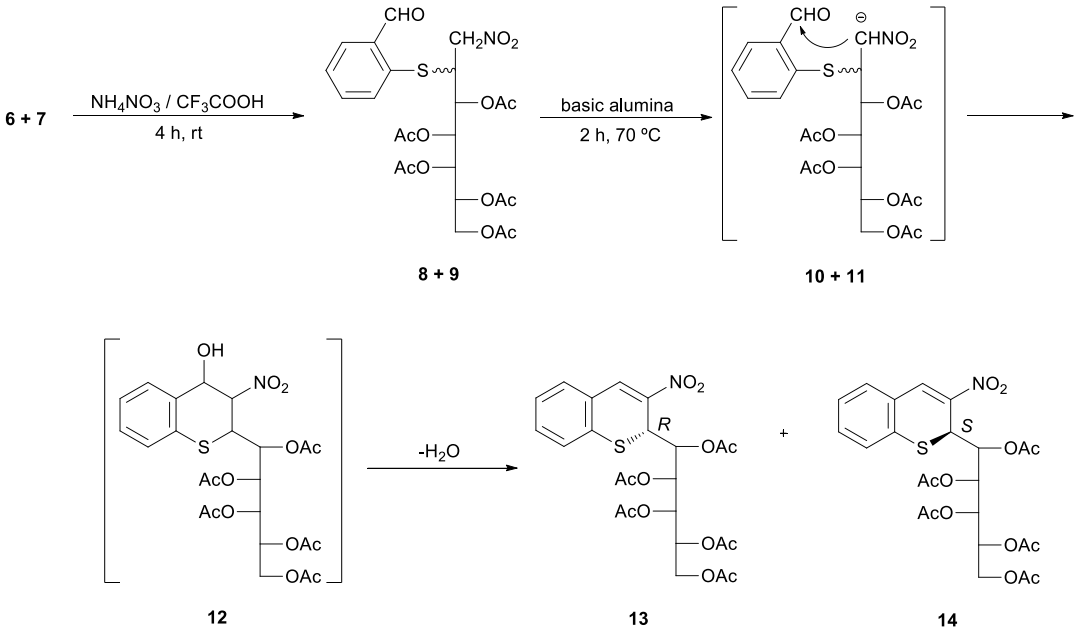
Reaction of the mixture **6**+**7** with ammonium nitrate in aqueous 90% trifluoroacetic acid led to the corresponding aldehydes **8**+**9** as a 0.8:1.0 mixture, which was subsequently embedded in activated basic alumina, thus yielding 3-nitro-2*H*-thiochromenes **13** and **14** (Scheme 3); from this mixture, diastereoisomer **13** crystallized from methanol, whereas oily **14** could be isolated by preparative thin layer chromatography (PTLC). As shown in Scheme 3, formation of these thiochromenes from aldehydes **8**+**9** could be justified by a Henry intramolecular reaction of carbanions **10**+**11**; then, dehydration of the resulting diastereoisomeric mixture of bicyclic alcohols **12** led to 3-nitro-2*H*-thiochromenes **13**+**14**.

Assignment of the absolute configuration at C-2 of 3-nitro-2*H*-thiochromene **13** was tentatively based on ^{1}H NMR spectroscopy, and determined unambiguously by X-ray diffraction analysis[23] (Figure 2); thus, the remarkable shielding of one of the methyl acetate groups (1.43 ppm) assigned to the acetate at C-1´ of the sugar skeleton indicated strong shield compared to the other four ones (2.00-2.20 ppm).



1 5 6 7

Scheme 2. Reaction between compounds **1** and **5**



Scheme 3. Formation of thiochromenes **13** and **14** from alcohols **6** and **7**

We suppose that the most shielded methyl group should be located on C-1´ of the carbohydrate chain, close to the shielding area of the aromatic ring.[24] Thus, it could be assumed that the preferred conformation in chloroform solution for **13** should be very similar to that is observed in solid state (Figure 2). In the case of compound **14** this effect was not detected, appearing the five signals of the methyl acetate groups at the normal predicted values, between 2.24 and 1.82 ppm.

Reaction between (*E*)-3,4,5,6,7-penta-*O*-acetyl-1-nitro-D-*manno*-nitrohept-1-enitol 15 and 2-mercaptobenzyl alcohol 5

The sulfa-Michael addition between nitroalkene **15** and 2-mercaptobenzyl alcohol **5** was carried out under solventless conditions, with DABCO as catalyst. After 40 min at 40 °C compound **16** was isolated in a very good yield (Scheme 4). From this result, we could conclude that the reaction was highly diastereoselective, being the absolute configuration at C-2 of **16** assigned by using the same arguments afore mentioned for compounds **3** and **4**.

Oxidation of the Michael adduct **16** was carried out at room temperature with ammonium nitrate in 90% trifluoroacetic acid. After 4 h, ^{1}H NMR from the crude product showed the presence of a 1:1 mixture of aldehydes **18** and **19** (Scheme 5), thus indicating epimerization at C-2.[17] Crystallization from methanol afforded pure acetal **21**, whereas **20** was isolated by PTLC from the mother liquor.

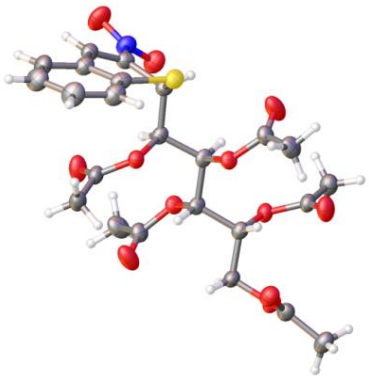
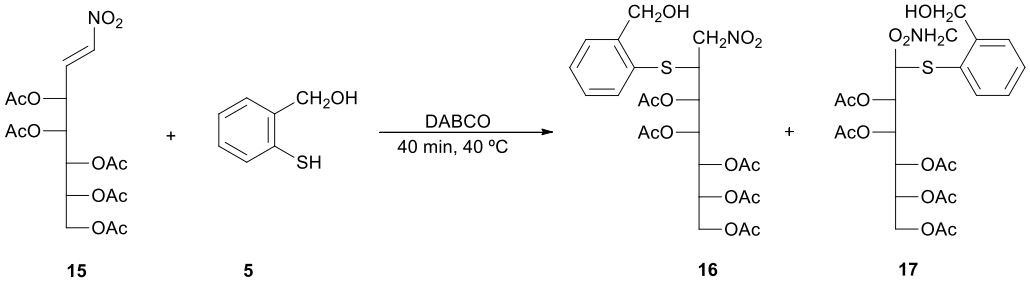
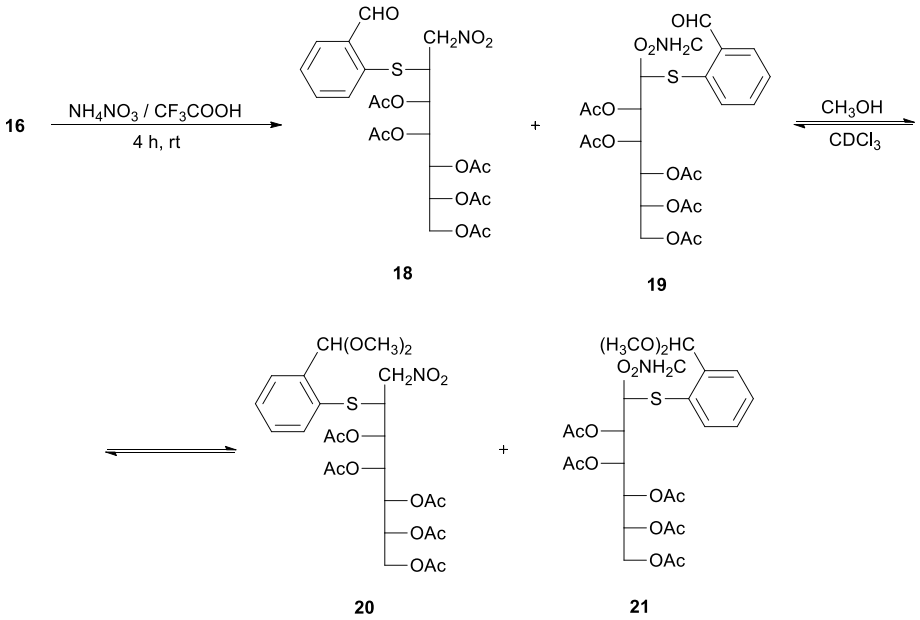


Figure 2. Solid state structure of **13**. Thermal ellipsoids drawn at the 50% probability level



Scheme 4. Reaction between **5** and **15**



Scheme 5. Oxidation of **16** and equilibrium between aldehydes and acetals

Structural assignment of **20** was based on the close analogy between ^{1}H NMR signals of its sugar-chain protons and those of compound **16**. It is worth mentioning that on standing chloroform solutions of **20** and **21** at room temperature for 7 days we observed, complete reversion from acetal **20** to aldehyde **18**; however, there was equilibrium between **21** and **19** (1.0:0.3 respective ratio).

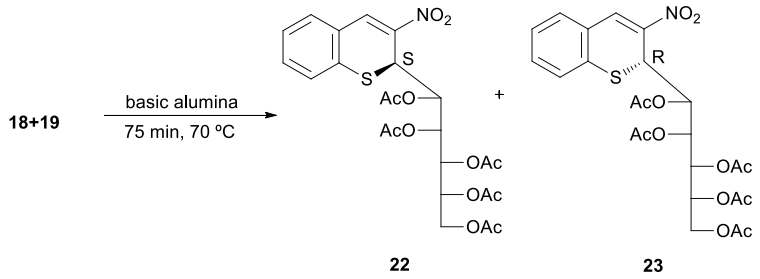
By heating with activated basic alumina, the mixture of aldehydes **18**+**19** yielded 3-nitro-2*H*-thiochromenes **22** and **23** (Scheme 6), which were separated by PTLC. Formation of these products could be justified by a similar mechanism to that shown in Scheme 4 for **13** and **14**. Concerning ^{1}H NMR data, we found (at 1.78 ppm) a slightly shielded methyl acetate group in the spectrum of **22**; explanation of this fact would be similar to which above suggested for compound **13** but, in this case, this group should be located in a more external zone of the region shielded by the ring current. On the other hand, the five methyl acetate groups of **23** appeared at the expected values, between 2.02 and 2.24 ppm.

The absolute configurations at C-2 in **22** and **23** have been assigned taking into account the relationship we have found between the $J_{1',2}$ coupling constants values of a series of 3-nitro-2*H*-chromenes[25a] and those from 3-nitro-2*H*-thiochromenes described herein. Thus, if the configuration of C-1′ is *S*, those compounds with medium to large values of $J_{1',2}$ (6-10 Hz) a *S* configuration at C-2 should have been assigned, whereas it should be *R* when $J_{1',2}$ values were small (0-2 Hz).

On the contrary, if the configuration of C-1′ is *R*, the range of the coupling constants values are reversed with respect to the previous case; thus, the $J_{1',2}$ value in thiochromene **13** [C-2(*R*)] was 2.5 Hz, being 10.0 Hz [C-2(*S*)] in its epimer **14**, while compound **22** showed a $J_{1',2}$ value of 1.5 Hz [C-2(*S*)], being this 8.5 Hz in **23** [C-2(*R*)]. These results are supported by parallel studies with chromenes and 1,2-dihydroquinolines.[25]

Biological assays

Some sulfa-Michael adducts and thiochromenes prepared herein were screened for biological activities using three different assays: antioxidant activity (free radical and H_2O_2 scavenging), α-glucosidase inhibition and antiproliferative activity. The antiradical activity was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl, free radical) method.[26] At 250 μM concentration, compounds **4**, **13** and **16** exerted a moderate antiradical activity (39±3%, 23±2%, 37±2%). For derivatives **4** and **16**, the EC_{50} value was calculated, that is the concentration of the antioxidant required to scavenge 50% of the initial free radical (383.5±93.6 μM and 255.1±60.4 μM, respectively).



Scheme 6. Formation of thiochromenes **21** and **22**

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The scavenging capacity of derivatives against H_2O_2, an abundant Reactive Oxygen Species, was also measured using the methodology reported by Bahorun et al.[27] According to this procedure, derivatives **13** and **16** behaved as moderate H_2O_2 scavengers, with scavenging properties of 60.1±1.1% and 77.5±0.6%, respectively, at 1.0 mM concentration.

Several derivatives bearing a chromene skeleton have been reported[28] as α-glucosidase inhibitors, and thus, with potential antidiabetic applications. Inhibition assay revealed that only adduct **4** exhibited a weak inhibition of α-glucosidase (33% at 500 µM concentration).

Finally, the antiproliferative activity of compounds **1**, **3**, **4**, **13**, **15**, **16** was evaluated against a panel of six human solid tumor cell lines: A-549 (non-small cell lung), HBL-100, (breast), HeLa (cervix), SW1573 (non-small cell lung), as drug sensitive lines, T-47D (breast) and WiDr (colon) as drug resistant lines. Such evaluation was accomplished following the protocol of the National Cancer Institute (NCI) of the United States.[29] Compounds **1** and **15** have been included with comparative purposes.[20]

Data are depicted in Table 1, and are expressed in GI_{50}, that is, the concentration of the compound that inhibits 50% of the tumor cell growth.

Concerning diastereoisomeric sulfa-Michael adducts **3** and **4**, no differences were found, both exhibiting moderate antiproliferative activity against the six cell lines tested (15-47 µM).

Surprisingly, there was a great difference of activity between diasteroisomeric thiochromenes **13** and **16**. Thus, while compound **13** showed no appreciable activity at the highest concentration tested (100 µM), derivative **16** was found to be a moderate antiproliferative agent (GI_{50} 25-35 µM). Remarkably derivative **16** showed a similar or even improved potency as 5-fluorouracil,[30] a widely-used chemotherapeutic agent against HeLa, T-47D and WiDr cells. This result suggests the importance of the configuration at C-2 on mentioned activity.

However, the most active compounds of the series were **1** and **15**, exhibiting GI_{50} values against all cells in the range 1.7-19 µM. Compound **1** is especially important, because shows a better antiproliferative profile against SW1573 and WiDr cell lines than 5-fluorouracil.

Results depicted in Table 1 support Castañedo *et al.* predictions,[18] because adducts **3** and **4** are more inactive than *trans*-nitroalkenes **1** and **15**.

On the other hand, carbohydrate chain at C-2 decreases the antiproliferative activity of thiochromenes **13** and **16** against A-549 cells with respect to unsubstituted ones.[31]

Table 1: Inhibitory effect of selected compounds on the growth of tumor cell lines

Compound	A-549	HBL-100	HeLa	SW1573	T-47D	WiDr
	$GI_{50} \pm s_D$ values(µM)[a]					
1	17 ± 3.8	14 ± 1.7	16 ± 1.8	1.7 ± 0.68	19 ± 1.6	18 ± 2.7
15	20 ± 2.1	10 ± 2.4	18 ± 0.5	2.1 ± 0.4	22 ± 3.5	24 ± 4.6
3	37 ± 13	25 ± 7.4	15 ± 3.6	32 ± 3.5	27 ± 2.9	35 ± 4.1
4	42 ± 17	28 ± 7.2	16 ± 4.3	47 ± 6.8	28 ± 5.6	33 ± 5.0
13	>100	>100	>100	>100	>100	>100
16	25 ± 7.7	28 ± 7.9	25 ± 9.2	28 ± 3.4	30 ± 5.5	35 ± 6.0
5-fluorouracil	Not tested	5.5 ± 2.3	15 ± 4.7	4.3 ± 1.6	47 ± 18	49 ± 6.7

[a]Values are means of two or three experiments

Experimental Section

Materials and Methods

Preparative TLC was performed using silica gel (Merck 60 GF_{254}). TLC was carried out on precoated Merck Kieselgel 60 GF_{254} aluminum backed plates; spots were visualized by UV light or iodine vapour. NMR spectra were taken either on a Bruker AC/PC instruments (500 MHz for ^1H and 125 MHz for ^{13}C) with tetramethylsilane as internal reference and deuteriochloroform as solvent. Coupling constant values are recorded in Hz. Characterization of NMR signals is based on homonuclear double-resonance and DEPT experiments. High resolution mass spectra were recorded on an Autoespec (Micromass) spectrometer, at the Centro de Investigación Tecnológica e Innovación (CITIUS) from Universidad de Sevilla Infrared spectra were recorded on a IR3000 Thermo Electron Corporation spectrophotometer in the range between 4000 and 600 cm^{-1}.

Antiradical activity was evaluated using the DPPH method:[26] the absorbance of methanolic solutions containing DPPH and each

compound was measured at 515 nm using a UV-Vis spectrophotometer. For H_2O_2 scavenging,[27] the absorbance of solutions containing hydrogen peroxide, each compound and horseradish peroxidase was determined at 610 nm in a UV-Vis spectrophotometer. α-glucosidase inhibition assays[28] were carried out by measuring the absorbance at 400 nm of DMSO-solutions of *p*-nitrophenyl-α-D-glucopyranoside (pH=6.8) and each compound (500 μM), also in a UV-Vis spectrophotometer. Evaluation of the antiproliferative activity was accomplished following the protocol of the NCI of the United States.[29] For each compound the cells were exposed to serial decimal dilutions in the range 0.001-100 μM for a period of 48 h. After exposure the SRB method was applied, determining the optical density of each well at 530 (main) and 620 nm (secondary). For each product concentration the percentage of growth (PG) according to the NCI formulas was calculated.

Procedures

3,4,5,6,7-Penta-*O*-acetyl-2-[(2´-ethoxy-2´-oxoethyl)thio]-D-*glycero*-L-*gluco*-1-nitroheptane 3 and 3,4,5,6,7-penta-*O*-acetyl-2-[(2´-ethoxy-2´-oxoethyl)thio]-D-*glycero*-L-*manno*-1-nitroheptane 4. A mixture of nitroalkene **1**[32] (2.5 g, 5.77 mmol), ethyl thioglycolate **2**[33] (1.3 mL, 11.86 mmol) and DABCO (0.32 g, 2.89 mmol) was stirred at 40 °C for 1.5 h. Then, TLC (1:2 hexane-diethyl ether) showed that the reaction had been completed, and the crude product was purified by silica gel column chromatography (1:2 hexane-diethyl ether). Evaporation of the appropriate fractions yielded a 0.8:1.0 oily mixture of **3**+**4** (2.87 g, 90%), which could be separated by fractional crystallization from methanol.

3: Mp 83-84 °C; IR: ν_{max} (KBr) 2967, 2915 (C-H), 1751, 1711 (C=O), 1556, 1370 (NO_2), 1208, 1027 (C-O), 629, 608 (C-S). ^{1}H NMR δ: 5.47 (dd, 1H, $J_{3,4}$ = 2.0 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 5.29 (m, 3H, H-3, H-5, H-6), 4.71 (dd, 1H, $J_{1a,1b}$ = 14.5 Hz, $J_{1a,2}$ = 7.0 Hz, H-1a), 4.59 (dd, 1H, $J_{1b,2}$ = 7.0 Hz, H-1b), 4.29 (dd, 1H, $J_{7a,7b}$ = 12.0 Hz, $J_{6,7a}$ = 5.0 Hz, H-7a), 4.21 (q, 2H, $COOCH_2$), 3.83 (dd, 1H, $J_{6,7b}$ = 7.5 Hz, H-7b), 3.75 (m, 1H, $J_{2,3}$ = 13.0 Hz, H-2), 3.30 (d, 1H, $J_{SCH2gem}$ = 15.0 Hz, SCH_2), 3.26 (d, 1H, SCH_2), 2.16 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.29 (t, 3H, $J_{CH3,CH2}$ = 7.0 Hz, CH_2CH_3). ^{13}C NMR δ: 170.4, 170.3, 170.3, 170.2, 169.8, 169.4 ($OCOCH_3$, $COOCH_2CH_3$), 75.6 (C-1), 68.5, 68.3, 67.9, 67.5 (C-3, C-4, C-5, C-6), 62.2 (C-7), 44.8 (C-2), 34.4 (CH_2CH_3), 20.9, 20.7, 20.6, 20.5, 20.4 ($OCOCH_3$), 14.0 (CH_2CH_3). Anal. Calcd for $C_{21}H_{31}NO_{14}S$: C, 45.57; H, 5.64; N, 2.53; S, 5.79. Found: C, 45.24; H, 5.48; N, 2.51; S, 5.83.

4: Mp 92-93 °C; IR: ν_{max} (KBr) 2979, 2961, 2937 (C-H), 1747, 1723 (C=O), 1562, 1372 (NO_2), 1215, 1027 (C-O), 613, 596 (C-S). ^{1}H NMR δ: 5.67 (dd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{3,4}$ = 1.5 Hz, H-4), 5.27 (m, 1H, H-6), 5.23 (dd, 1H, $J_{5,6}$ = 2.0 Hz, H-5), 5.07 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-3), 4.70 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 4.5 Hz, H-1a), 4.50 (dd, 1H, $J_{1b,2}$ = 9.5 Hz, H-1b), 4.27 (dd, 1H, $J_{7a,7b}$ = 11.5 Hz, $J_{6,7a}$ = 5.0 Hz, H-7a), 4.20 (q, 2H, $J_{CH2,CH3}$ = 7.0 Hz, $COOCH_2$), 3.83 (dd, 1H, $J_{6,7b}$ = 7.5 Hz, H-7b), 3.62 (m, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.50 (d, 1H, $J_{SCH2gem}$ = 15.5 Hz, SCH_2), 3.36 (d, 1H, SCH_2), 2.18 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.29 (t, 3H, $J_{CH3,CH2}$ = 7.0 Hz, CH_2CH_3). ^{13}C NMR δ: 170.9, 170.6, 170.4, 170.3, 169.8, 169.7 ($OCOCH_3$, $COOCH_2CH_3$), 76.4 (C-1), 70.6 (C-3), 67.8, 67.70, 67.3 (C-4, C-5, C-6), 62.1 (C-7), 43.2 (C-2), 34.2 (CH_2CH_3) 20.7, 20.6, 20.5, 20.3 ($OCOCH_3$), 14.0 (CH_2CH_3). Anal. Calcd for $C_{21}H_{31}NO_{14}S$: C, 45.57; H, 5.64; N, 2.53; S, 5.79. Found: C, 45.49; H, 5.49; N, 2.60; S, 5.61.

(2*R*)-3-Nitro-(1´,2´,3´,4´,5´-penta-*O*-acetyl-D-*galacto*-pentitol-1´-yl)-2*H*-thiochromene 13 and (2*S*)-3-nitro-(1´,2´,3´,4´,5´-penta-*O*-acetyl-D-*galacto*-pentitol-1´-yl)-2*H*-thiochromene 14. A mixture of nitroalkene **1**[32] (0.5 g, 1.15 mmol), 2-mercaptobenzyl alcohol **5**[34] (0.15 mL, 1.30 mmol) and DABCO (65 mg, 0.58 mmol) was stirred at 40 °C. After 30 min, TLC (1:3 hexane-diethyl ether) showed that the reaction had been completed, and the crude product was purified by column chromatography with 1:3 hexane-diethyl ether as eluant. Evaporation of fractions containing **6**+**7** led to an oily residue from which an inseparable 0.7:1 mixture of the adducts **6**+**7** crystallized from methanol (0.49 g, 74%); then, 0.10 g (0.17 mmol) of this solid mixture was stirred at room temperature for 4 h with ammonium nitrate (3.0 mg, 0.04 mmol) in 90% trifluoroacetic acid[35](1.7 mL). The reaction crude was diluted with water (17 mL) and extracted with dichloromethane (4 x 75 mL); the combined organic extracts were dried with anhydrous sodium sulfate, filtered, and evaporated to yield 80 mg (76%) of a (0.8:1.0) oily mixture of **8** and **9**.

Subsequently, a mixture of **8** and **9** (150 mg, 0.26 mmol) with activated basic alumina (0.26 g, 2.55 mmol) was stirred at 70 °C for 2 h. Then, methanol (10 mL) was added, the alumina filtered, and the solution evaporated to an oily mixture (0.11 g, 77%) of **13** and **14**, from which 25 mg (52%) of the former compound crystallized from methanol. An analytical sample of pure diastereomer **14** was isolated by PTLC with 1:3 hexane-diethyl ether as eluant.

13: Mp 187-188 °C; IR: ν_{max} (KBr) 3057, 3024, 2959 (C-H), 1748, 1735 (C=O), 1647 (C=C), 1522, 1371 (NO_2), 1207, 1036 (C-O), 768, 602 (C-S). ^{1}H NMR δ: 7.93 (s, 1H, H-4), 7.36 (m, 3H, H-5, H-7, H-8), 7.21 (td, 1H, H-6), 5.42 (dd, 1H, $J_{2´,3´}$ = 12.0 Hz, $J_{1´,2´}$ = 3.0 Hz, H-2´), 5.32 (dd, 1H, $J_{1´,2}$ = 2.5 Hz, H-1´), 5.30 (m, 1H, H-4´), 5.23 (dd, 1H, $J_{3´,4´}$ = 2.5 Hz, H-3´), 4.78 (d, 1H, H-2), 4.23 (dd, 1H, $J_{5´a,5´b}$ = 14.5 Hz, $J_{4´,5´a}$ = 6.0 Hz, H-5´a), 3.80 (dd, 1H, $J_{4´,5´b}$ = 9.0 Hz, H-5´b), 2.21 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.43 (s, 3H, OAc). ^{13}C NMR δ: 170.5, 170.4, 170.3, 170.2, 169.9 ($OCOCH_3$), 141.3 (C-8a), 133.6 (C-3), 133.3, 132.4, 131.9 (C-4, C-5, C-7), 126.9, 126.5 (C-6, C-8), 128.1 (C-4a), 69.5, 68.9, 67.8, 67.5 (C-1´, C-2´, C-3´, C-4´), 62.1 (C-5´), 39.0 (C-2), 21.3, 20.8, 20.6, 20.5, 19.6 ($OCOCH_3$). HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{27}O_{12}NNaS$ 576.1146; found 576.1132.

14: ^{1}H NMR δ: 7.96 (s, 1H, H-4), 7.48, 7.44 (each d, 1H, $J_{5,6}$ = $J_{7,8}$ = 7.0 Hz, H-5, H-8), 7.39, 7.31 (each t, 1H, $J_{6,7}$ = 7.0 Hz, H-6, H-7), 5.71 (dd, 1H, $J_{2´,3´}$ = 9.5 Hz, H-2´), 5.30 (m, 1H, H-4´), 5.16 (dd, 1H, $J_{3´,4´}$ = 2.0 Hz, H-3´), 5.07 (dd, 1H, $J_{1´,2´}$ = 1.0 Hz, H-1´), 4.49 (d, 1H, $J_{1´,2}$ = 10.0 Hz, H-2), 4.23 (dd, 1H, $J_{5´a,5´b}$ = 12.0 Hz, $J_{4´,5´a}$ = 5.0 Hz, H-5´a), 3.81 (dd, 1H, $J_{4´,5´b}$ = 7.5 Hz, H-5´b), 2.24 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.93 (s, 3H, OAc), 1.82 (s, 3H, OAc). ^{13}C NMR δ: 170.6, 170.4, 170.2, 169.7, 169.5 ($OCOCH_3$), 141.0 (C-8a), 132.5, 132.2, 132.0 (C-4, C-5, C-7), 131.1 (C-3), 128.4 (C-4a), 127.7, 127.0 (C-6, C-8), 69.8, 67.9, 67.7, 66.2 (C-1´, C-2´, C-3´, C-4´), 62.2 (C-5´), 34.8 (C-2), 20.7, 20.6, 20.3, 20.2 ($OCOCH_3$). HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{27}O_{12}NNaS$ 576.1146; found 576.1132.

3,4,5,6,7-Penta-*O*-acetyl-2-[(2´-hydroxymethylphenyl)-thio]-D-*glycero*-D-*talo*-1-nitroheptane 16. A mixture of nitroalkene **15**[36] (0.5 g, 1.15 mmol), 2-mercaptobenzyl alcohol **5**[34] (0.15 mL, 1.30 mmol) and DABCO (60 mg, 0.58 mmol) was stirred at 40 °C. After 40 min TLC (1:3 hexane-diethyl ether) showed that the reaction had been completed, being isolated the pure compound **16** by crystallization from methanol (0.58 g, 87%).

16: Mp 126-127 °C; IR: ν_{max} (KBr) 3496, 3443 (O-H), 3060, 3018, 2972, 2956 (C-H), 1739, 1716 (C=O), 1563, 1372 (NO_2), 1217, 1047 (C-O), 761, 609 (C-S). ^{1}H NMR δ: 7.61, 7.52 (each dd, 1H, H-2´, H-5´), 7.39, 7.34 (each td, 1H, H-3´, H-4´), 5.40 (dd, 1H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 5.34 (dd, 1H, $J_{2,3}$ = 4.0 Hz, H-3), 5.33 (dd, 1H, $J_{5,6}$ = 8.5 Hz, H-5), 5.00 (m, 1H, H-6), 4.83 (d, 1H, $J_{1´a,1´b}$ = 12.5 Hz, CH_2OH), 4.79 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 9.0 Hz, H-1a), 4.75 (d, 1H, CH_2OH), 4.45 (dd, 1H, $J_{1b,2}$ = 4.5 Hz, H-1b), 4.17 (dd, 1H, $J_{7a,7b}$ = 12.5 Hz, $J_{6,7a}$ = 2.5 Hz, H-7a), 4.11 (m, 1H, H-2), 3.98 (dd, 1H, $J_{6,7b}$ = 5.0 Hz, H-7b), 2.46 (bt, 1H, OH), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc). ^{13}C NMR δ: 170.5, 170.2, 169.9, 169.8, 169.7 (O*C*OCH$_3$), 143.8 (C-1´), 134.5 (C-2´), 130.2, 129.9, 129.5, 128.9 (C-3´, C-4´, C-5´, C-6´), 75.2 (C-1), 70.4 (C-3), 68.3, 68.0, 67.3 (C-4, C-5, C-6), 63.2 (CH_2OH), 61.8 (C-7), 47.1 (C-2), 20.8, 20.7, 20.6, 20.5 (OCO*C*H$_3$). HRMS (ESI) calcd for $C_{24}H_{31}O_{13}NNaS$ $[M+Na]^+$ 596.1408; found 596.1395.

3,4,5,6,7-Penta-*O*-acetyl-2-[(2´-dimethoxymethylphenyl)-thio]-D-*glycero*-D-*talo*-1-nitroheptane 20 and 3,4,5,6,7-penta-*O*-acetyl-2-[(2´-dimethoxymethylphenyl)thio]-D-*glycero*-D-*galacto*-1-nitroheptane 21, 3,4,5,6,7-penta-*O*-acetyl-2-[(2´-formyl-phenyl)thio]-D-*glycero*-D-*talo*-1-nitroheptane 18 and 3,4,5,6,7-penta-*O*-acetyl-2-[(2´-formylphenyl)thio]-D-*glycero*-D-*galacto*-1-nitroheptane 19. A mixture of **16** (0.10 g, 0.17 mmol) and ammonium nitrate (3.0 mg, 0.04 mmol) in 90% trifluoroacetic acid[35] (1.7 mL) was stirred at room temperature for 4 h. Then, the reaction crude was diluted with water (17 mL) and extracted with dichloromethane (4 x 75 mL); the combined organic extracts were dried with anhydrous sodium sulfate, filtered, and evaporated to yield 73 mg (74%) of **18** and **19** as a 1:1 oily mixture from which 10 mg of acetal **21** crystallized from methanol. An analytical amount of diastereomer **20** was isolated by PTLC of the mother liquor with 1:3 hexane-diethyl ether as eluant.

On standing in deuteriochloroform solution for a week at room temperature, complete reversion of acetal **20** to aldehyde **18** was observed. Under similar conditions, there was only partial conversion of **21** to **19** (1.0:0.3 respective ratio).

20: ^{1}H NMR δ: 7.65 (m, 2H, H-3´, H-6´), 7.38 (m, 2H, H-4´, H-5´), 5.72 (s, 1H, C*H*(OCH$_3$)$_2$, 5.43 (dd, 1H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 2.5 Hz, H-4), 5.37 (dd, 1H, $J_{5,6}$ = 8.5 Hz, H-5), 5.35 (dd, 1H, H-3), 5.05 (m, 1H, H-6), 4.70 (dd, 1H, $J_{1a,2}$ = 5.5 Hz, $J_{1a,1b}$ = 14.0 Hz, H-1a), 4.45 (dd, 1H, $J_{1b,2}$ = 8.0 Hz, H-1b), 4.18 (dd, 1H, $J_{6,7a}$ = 2.5 Hz, $J_{7a,7b}$ = 12.5 Hz, H-7a), 4.08 (m, 1H, H-2), 4.00 (dd, 1H, $J_{6,7b}$ = 5.0 Hz, H-7b), 3.36, 3.34 (each s, each 3H, 2 x OCH$_3$), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc). ^{13}C NMR δ: 170.5, 170.2, 169.9, 169.8, 169.4 (O*C*OCH$_3$), 140.7 (C-1´), 134.1, (C-2´), 130.6, 129.4, 128.8, 127.8 (C-3´, C-4´, C-5´, C-6´), 101.1 (*C*H(OCH$_3$)$_2$), 75.3 (C-1), 70.3 (C-3), 68.4, 67.9, 67.2 (C-4, C-5, C-6), 61.9 (C-7), 53.5, 53.3 (O*C*H$_3$)$_2$, 46.9 (C-2), 20.8, 20.7, 20.6, 20.5, 20.4 (OCO*C*H$_3$).

21: Mp 131-132 °C; ^{1}H NMR δ: 7.64, 7.56 (each dd, 1H, H-3´, H-6´), 7.36 (m, 2H, H-4´, H-5´), 5.82 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 5.72 (s, 1H, C*H*(OCH$_3$)$_2$, 5.46 (dd, 1H, $J_{5,6}$ = 9.0 Hz, H-5), 5.24 (dd, 1H, $J_{2,3}$ = 1.5 Hz, H-3) 5.06 (m, 1H, H-6), 4.65 (dd, 1H, $J_{1a,2}$ = 10.0 Hz, $J_{1a,1b}$ = 14.0 Hz, H-1a), 4.36 (dd, 1H, $J_{1b,2}$ = 4.5 Hz, H-1b), 4.23 (dd, 1H, $J_{6,7a}$ = 2.5 Hz, $J_{7a,7b}$ = 12.5 Hz, H-7a), 4.10 (m, 1H, H-2), 4.06 (dd, 1H, $J_{6,7b}$ = 5.0 Hz, H-7b), 3.40, 3.25 (each s, each 3H, 2 x OCH$_3$), 2.18 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc). ^{13}C NMR δ: 170.5, 170.2, 170.1, 169.9, 169.8 (O*C*OCH$_3$), 140.3 (C-1´), 133.8 (C-2´), 130.6, 129.7, 128.5, 127.8 (C-3´, C-4´, C-5´, C-6´), 100.6 (*C*H(OCH$_3$)$_2$), 75.1 (C-1), 68.8, 68.0, 67.9, 67.6 (C-3, C-4, C-5, C-6), 61.8 (C-7), 53.7, 52.1 (O*C*H$_3$)$_2$, 47.3 (C-2), 20.9, 20.8, 20.7, 20.6, 20.5 (OCO*C*H$_3$). MS (ESI): m/z =586 (M-OMe), 512 (M- 2OMe-Ac).

18: ^{1}H NMR δ: 10.35 (s, 1H, CHO), 7.87 (dd, 1H, H-3´), 7.58 (m, 2H, H-5´, H-6´), 7.43 (td, 1H, H-4´), 5.37 (dd, 1H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 2.0 Hz, H-4) 5.26 (m, 2H, H-3, H-5), 4.96 (m, 1H, H-6), 4.72 (dd, 1H, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 5.5 Hz, H-1a), 4.38 (dd, 1H, $J_{1b,2}$ = 8.0 Hz, H-1b), 4.09 (dd, 1H, $J_{7a,7b}$ = 12.5 Hz, $J_{6,7a}$ = 3.0 Hz, H-7a), 4.06 (m, 1H, H-2), 3.91 (dd, 1H, $J_{6,7b}$ = 5.5 Hz, H-7b), 2.10 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.97 (s, 3H, OAc), 1.95 (s, 3H, OAc). ^{13}C NMR δ: 191.1 (CHO), 170.5, 170.1, 169.9, 169.8, 169.3 (O*C*OCH$_3$), 136.4, 135.8 (C-1´, C-2´), 134.5, 132.7, 131.4, 128.6 (C-2´, C-3´, C-4´, C-5´), 75.0 (C-1), 69.6 (C-3), 68.4, 67.8, 67.1 (C-4, C-5, C-6), 61.8 (C-7), 46.7 (C-2), 20.8, 20.6, 20.5, 20.4 (OCO*C*H$_3$).

19 (signals from the mixture **19**+**21**): ^{1}H NMR δ: 10.46 (s, 1H, CHO), 7.94, 7.63 (each dd, 1H, H-3´, H-6´), 7.48, 7.19 (each td, 2H, H-4´, H-5´), 5.77 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 5.49 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 5.25 (dd, 1H, $J_{2,3}$ = 1.5 Hz, H-3), 5.08 (m, 1H, H-6), 4.76 (dd, 1H, $J_{1a,1b}$ = 14.5 Hz, $J_{1a,2}$ = 9.0 Hz, H-1a), 4.45 (dd, 1H, $J_{1b,2}$ = 5.5 Hz, H-1b), 4.23 (dd, 1H, $J_{7a,7b}$ = 12.5 Hz, $J_{6,7a}$ = 3.0 Hz, H-7a), 4.12 (m, 1H, H-2), 4.07 (dd, 1H, $J_{6,7b}$ = 5.0 Hz, H-7b), 2.19 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc).

(2*S*)-3-Nitro-(1´,2´,3´,4´,5´-penta-*O*-acetyl-D-*manno*-pentitol-1´-yl)-2*H*-thiochromene 22 and (2*R*)-3-nitro-(1´,2´,3´,4´,5´-penta-*O*-acetyl-D-*manno*-pentitol-1´-yl)-2*H*-thiochromene 23. A mixture of aldehydes **18**+**19** (0.15 g, 0.26 mmol) with activated basic alumina (0.26 g, 2.55 mmol) was stirred at 70 °C for 75 min. Then, methanol (10 mL) was added, the alumina was filtered, and the solution was evaporated, leading to an oily mixture (0.13 g, 88%) of **22** and **23**. Analytical samples of each one of these compounds were obtained pure by PTLC with 1:3 hexane-diethyl ether as eluant.

22: ^{1}H NMR δ: 8.00 (s, 1H, H-4), 7.46 (d, 1H, H-5), 7.39 (td, 1H, H-7), 7.35 (dd, 1H, H-8), 7.21 (td, 1H, H-6), 5.83 (dd, 1H, $J_{1´,2´}$ = 10.0 Hz, $J_{2´,3´}$ = 2.0 Hz, H-2´), 5.38 (dd, 1H, $J_{3´,4´}$ = 9.5 Hz, H-3´), 5.27 (dd, 1H, $J_{1´,2}$ = 1.5 Hz, H-1´), 5.15 (m, 1H, H-4´), 4.44 (dd, 1H, H-2), 4.19 (dd, 1H, $J_{4´,5´a}$ = 3.0 Hz, $J_{5´a,5´b}$ = 12.5 Hz, H-5´a), 4.05 (dd, 1H, $J_{4´,5´b}$ = 5.5 Hz, H-5´b), 2.24 (s, 3H, OAc), 2.16 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc). ^{13}C NMR δ: 170.6, 170.5, 169.9, 169.8 (O*C*OCH$_3$), 140.9 (C-8a), 133.9, 132.4, 131.9 (C-4, C-5, C-7),

133.8 (C-3), 127.9 (C-4a), 126.7, 126.2 (C-6, C-8), 70.1 (C-1´), 67.8, 67.3, 66.8 (C-2´, C-3´, C-4´), 61.9 (C-5´), 37.9 (C-2), 20.9, 20.7, 20.6, 20.5, 20.2 (OCO*C*H$_3$). HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{24}H_{27}O_{12}NNaS$ 576.1146; found 576.1128.

23: ^{1}H NMR δ: 7.98 (s, 1H, H-4), 7.42 (dd, 2H, H-5, H-8), 7.38 (td, 1H, H-7), 7.28 (td, 1H, H-6), 5.56 (dd, 1H, $J_{1´,2´}$ = 6.0 Hz, $J_{2´,3´}$ = 3.5 Hz, H-2´), 5.52 (dd, 1H, $J_{3´,4´}$ = 8.0 Hz, H-3´), 5.19 (dd, 1H, $J_{1´,2}$ = 8.5 Hz, H-1´), 5.11 (m, 1H, H-4´), 4.94 (d, 1H, H-2), 4.23 (dd, 1H, $J_{4´,5´a}$ = 3.0 Hz, $J_{5´a,5´b}$ = 12.5 Hz, H-5´a), 4.07 (dd, 1H, $J_{4´,5´b}$ = 5.5 Hz, H-5´b), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.78 (s, 3H, OAc). ^{13}C NMR δ: 170.6, 169.9, 169.8, 169.6, 169.2 (O*C*OCH$_3$), 141.0 (C-8a), 132.2, 132.1, 132.0 (C-4, C-5, C-7), 130.9 (C-3), 128.5 (C-4a), 127.5, 127.0 (C-6, C-8), 71.5 (C-1´), 69.3, 68.3, 67.4 (C-2´, C-3´, C-4´), 61.6 (C-5´), 35.6 (C-2), 20.8, 20.7, 20.6, 20.5, 20.2 (OCO*C*H$_3$).

Conclusions

In conclusion, we have combined within this work sulfa-Michael addition reactions between carbohydrate-derived nitroalkenes and thiols with their transformation into 3-nitro-2*H*-thiochromenes as well as a study of the biological activity of some of the new products described herein. It has been also found that antiproliferative activity of new thiochromenes is lower than that of starting nitroalkenes, according to the results previously reported for chromenes and 1,2-dihydroquinolines,[25] and carbohydrate-derived amino-adducts.[20]

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