Synthesis of a Series of Hexitol and Aminodeoxyhexitol Mononitrate Derivatives Containing a Sulfur Group and Pharmacological Evaluation on Isolated Rat Aortas

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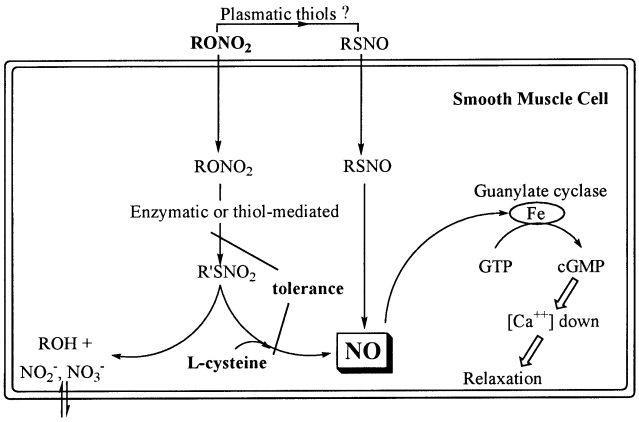
As part of our research into new organic nitrates for the treatment of angina pectoris, we have investigated a series of hexitol and aminodeoxyhexitol mononitrate derivatives containing a sulfur group. Since the depletion of tissue stores of sulfhydryl groups appears to play an important role in the development of this phenomenon, the addition of a sulfur group to a nitrate derivative could prevent the development of nitrate tolerance during a long-term treatment. Before studying the duration of action, and the possible influence on tolerance phenomenon, it was important to check the vasorelaxing effects of our compounds compared to those of commercial organic nitrates of similar structures such as isosorbide mononitrate or isosorbide dinitrate. All the compounds were tested on isolated rat aortas; some of these products exhibited an interesting activity.

Organic nitrates, for example nitroglycerin, constitute the most widely used treatment for angina pectoris. Although not conclusively demonstrated[1], it now seems well-documented that these compounds are transformed during the enzymatic or thiol-mediated metabolism as depicted in Figure 1; they induce, by release of nitric oxide, stimulation of soluble guanylate cyclase and consequently relaxation of vascular smooth muscle cells[2][3][4][5][6].

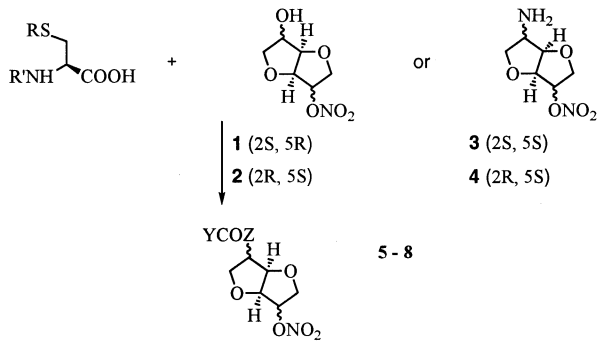
Figure 1. Postulated metabolism of organic nitrates and the development of nitrate tolerance



Nevertheless, in order to obtain a long-lasting effect, drugs have to be administered continuously, and this induces the development of tolerance which limits their efficiency. This has been explained by an intracellular depletion in thiol groups[7]. As it is known that the phenomenon can be avoided or reduced by simultaneous administration of L-cysteine derivatives[8][9][10], we have postulated that new compounds containing a nitrate moiety linked to cysteine, or masked cysteine, may provide the basis for structures devoid of tolerance development.

For the design of new drugs, we have decided to combine the most easily obtained hexitol mononitrates **1**, **2** and the aminodeoxyhexitol mononitrates **3**, **4** with L-cysteine derivatives (Figure 2). Due to the instability of the free S−H group, protected or masked cysteines were used for the different syntheses.

Figure 2. Syntheses of nitrate and deoxyhexitolnitrates and their derivatives (Y = thioamino acid part; Z = O or N)



  1434−193X/98/0505−0933 $ 17.50+.50/0

Chemistry

The pathway for our synthesis (Figure 2) consists of a coupling reaction between the acid group of L-cysteine derivatives and hydroxy or amino group of the hexitol moiety by means of 1,3-dicyclohexylcarbodiimide (DCC) or 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate as coupling agent (1-hydroxybenzotriazole is added to prevent racemization). Among the hexitol nitrates used, 1,4:3,6-dianhydro-D-glucitol-5-nitrate (**1**) is commercialy available and 1,4:3,6-dianhydro-D-glucitol-2-nitrate (**2**) is synthesized according to the procedure described by Hayward[11]. Among the deoxyhexitol nitrates, 5-amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (**3**) and 2-amino-2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate (**4**) are prepared according to the method described by Klessing[12]. From these starting materials, different products were obtained (Table 1). Compounds **5a**−**5d** were prepared with *S*-acetamidomethyl-*N*-*tert*-butoxycarbonyl)-L-cysteine. The Boc group is then easily removed in acidic medium to give the corresponding **6a**−**6d** derivatives (Table 1). Several attempts to remove the acetamidomethyl substituent under usual reaction conditions did not lead to stable compounds with a free SH group.

Table 1. Isolated and purified solid compounds

R	RCOO	RCOO	RCONH	RCONH
$CH_3CONHCH_2S$ $(CH_3)_3COCONH$	**5a** 73%	**5b** 46%	**5c** 94%	**5d** 44%
$CH_3CONHCH_2S$ $HCl.NH_2$	**6a** 85%	**6b** 88%	**6c** 55%	**6d** 83%
$(CH_3)_3COOC$	**7a** 51%	**7b** 60%	**7c**[a]	
$HCl.H$	**8a** 76%	**8b** 40%	**8c** 81%	**8d** 29%

[a] This oily compound was not pure enough to be tested.

Since Thiazolidine-4(*R*)-carboxylic acid (L-thioproline) is known to generate L-cysteine upon metabolism in the liver[13], we have synthesized compounds **7a**−**7c** (Table 1) by the reaction between *N*-*tert*-butoxycarbonylthiazolidine-4(*R*)-carboxylic acid (*N*-*t*Boc-L-thioproline) and the nitrate derivatives **1**−**4**. After treatment in an acidic medium, derivatives **8a**−**8c** are obtained (Table 1). *N*-*t*Boc-L-thioproline must be used rather than L-thioproline to avoid the formation of dioxopiperazines. Indeed the poor yield obtained in the preparation of **8d** is due to the direct reaction between L-thioproline and the aminonitrate **4**. It is interesting to note that no epimerisation occurred during these reactions.

Taking into account a very interesting activity in the pharmacological test for compound **8c**, we did not try to obtain the stable compound bearing a free SH group, but decided to investigate the coupling between 5-amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (**3**) and different substituted thioprolines. The compounds obtained are given in Table 2.

Since Ratner et al.[14] and Woodward et al.[15] have studied the stability of thioproline and shown the faster decomposition of 2,2-dimethylthioproline in aqueous medium to give cysteine and acetone, we decided to prepare **9** and **10** (Table 2). We determined, as indicated by the NMR spectra, that the ring-opening occurred slowly when **10** was in an H_2O or D_2O solution, in accord with previous results[15][16][17].

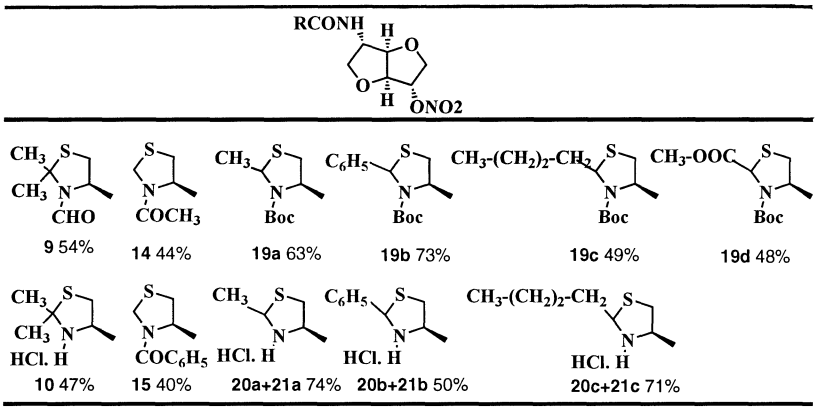
Attempts to isolate and purify **12** did not lead to a pure compound; only a mixture with an oxidized compound (probably **13**) as major component could be recovered (Figure 3). Compounds **14** and **15** (Table 2) were synthesized to evaluate the effect of acyl and benzoyl groups on activity. Different 2-substituted thioprolines were prepared by reaction of L-cysteine on the corresponding aldehydes[18][19] (Figure 4). With the use of results published by Szilagyi et al.[19], the mixtures of two diastereomers in various ratios [**16a/17a** (CH_3): 35:65; **16b/17b** (C_6H_5): 40:60; **16c/17c** (*n*-C_4H_9): 50:50] were determined by comparison of their ^{1}H-NMR spectra with that of the compound **16d** (2*R*, 4*R*), obtained according to the method of Baxter et al.[20].

When *tert*-butoxycarbonyl was used as the *N*-protecting group, only one diastereomer (**18a**−**18d**) was obtained. The configuration of each compound was determined by analogy with the results of Szilagyi[19], who measured the sum ($J_{4\text{-H},5\text{-H}} + J_{4\text{-H},5'\text{-H}}$) = 12.5 Hz (at 100°C in [D$_6$]DMSO) for *cis*-3-acetyl-2(*R*)-phenylthiazolidine-4(*R*)-carboxylic acid and 6.5 Hz for *trans*-3-acetyl-2(*S*)-phenylthiazolidine-4(*R*)-carboxylic acid. In our compounds, this sum of coupling constants equals 13.5 Hz for **18a**, 13 Hz for **18b** in [D$_6$]DMSO, and 14.2 Hz for **18c** in C_5D_5N. All these compounds were therefore assigned *cis* isomers. Each thiazolidinecarboxylic acid derivative **18a**−**18d** reacted with **3** and gave only one diastereomer, **19a**−**19d**. From the sums ($J_{7\text{-H},8\text{-H}} + J_{7\text{-H},8'\text{-H}}$) = 14.7 Hz for **19a**, 13.5 Hz for **19b**, 15.6 Hz for **19c** and 13 Hz for **19d**, (2*R*) and (4*R*) configurations were attributed to asymmetric centers of the thiazolidine ring. After treatment in acidic medium (HCl in MeCOOEt), compounds **19** gave a mixture of two diastereomers **20** and **21** due to an interconversion via the Schiff base (Figure 4).

Pharmacological Results

An in vitro test was used to investigate the pharmacological activity of our products. Vasorelaxation was evaluated in vitro by means of a test on isolated rat aortas without endothelium and precontracted with norepinephrine[21][22]. The relaxation caused by different substances was measured upon addition of increasing doses of each compound; this relaxation was calculated with reference to the maximal contraction obtained with norepinephrin (0.1 μM). Struc-

Table 2. Synthesized compounds according to the following R moieties



[a] This oily compound was not pure enough to be tested.

Figure 3. Hydrolysis of compound **10** leading to **12** and further, by oxidation, to disulfide **13**

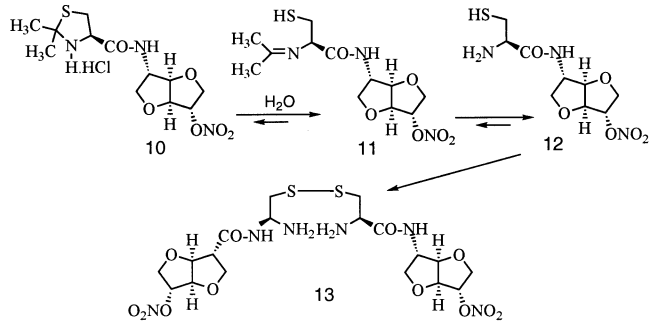
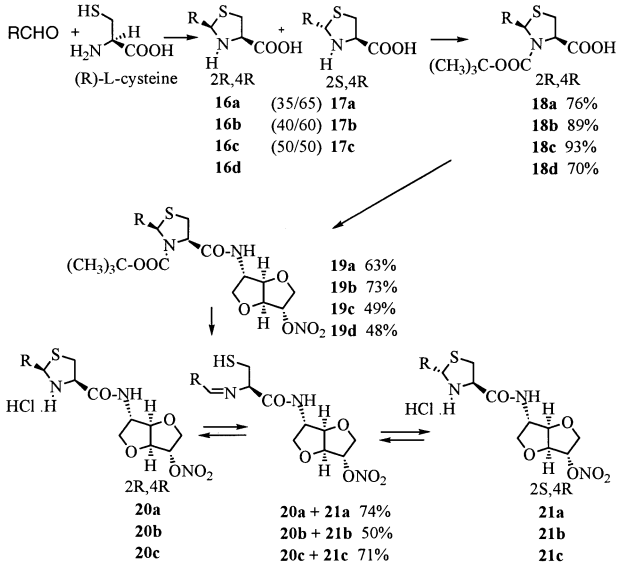


Figure 4. Syntheses of compounds **16**, **17**, **18**, **19**, and mixtures of **20** + **21** (**a**: R = CH_3; **b**: R = C_6H_5; **c**: R = n-C_4H_9; **d**: R = $COOCH_3$)



tures giving a relaxation higher than 80% with an IC_{50} lower than 20 μM were of particularly interest. In Table 3, we noted that these critera were obtained with compound **8c** (IC_{50} = 10 μM and maximal relaxation = 100%) in the first group of compounds (Table 1), and with compounds **11**, **14**, **15**, **19a** and with mixtures **20a** + **21a**, **20b** + **21b**, and **20c** + **21c** in the second group (Table 2), the mixture **20b** + **21b** giving the strongest effect. Results concerning relaxation of isolated rat aortas are given in Table 3; compared to IS-5MN (isosorbide mononitrate), the most used and commercialy available mononitrate, some of our products exhibited greater activity (Table 3); compared to ISDN (isosorbide dinitrate), only the mixture **20b** + **21b** is more interesting. Our compounds proved less active than nitroglycerin which is known to have a very strong effect but also only a short-term activity. It is noticeable that compound **8c**, which results from the reaction of **3** and thioproline, has a better effect than **3** or the mixture of **3** and thioproline.

Conclusion

This study presents a series of new organic nitrates containing thiol groups. Several of these compounds had greater vasorelaxing effects than isosorbide mononitrate, and one of them has a good effect compared to isosorbide dinitrate. The most interesting compounds will be evaluated to determine their duration of action and, therefore, will be investigated in a pharmacological model for tolerance in the dog.

Experimental Section

Melting points were determined with a Büchi apparatus and are uncorrected. All compounds are colorless. − Optical rotations were measured in solution with a Perkin Elmer 241 polarimeter. − IR spectra were recorded with a Perkin Elmer 1720 X FT-IR spectrometer (KBr pellets for solids and films for liquids). − ^{1}H-NMR spectra were recorded at 200 MHz with a Bruker AC 200 spectrometer or at 300 MHz with a Bruker AM 300 spectrometer. TMS was used as internal reference standard. The numbering of the different hydrogen atoms is indicated in Table 1. − Microanalyses were performed by Société Française Hoechst or Service Central d′Analyse du C.N.R.S. and results obtained were within ± 0.4% of the calculated values except for compounds **6b** and **10**. Most of our compounds contained water, which was detected by ^{1}H-NMR spectroscopy. The presence of water was also confirmed by Karl Fischer analyses for some of them. This is the reason why some of

Table 3. Relaxation of isolated rat aortas (without endithelium) precontracted with 0.1μM norepinephrine ($n = 2-3$); IS-5-MN: isosorbide-5-mononitrate; ISDN: isosorbide-2,5-dinitrate; NTG: nitroglycerine

Compound	IC50 (μM)	Max. Relaxation [%]
5a	28	85
5b	80	70
5c	>100	50
5d	63	70
6a	100	31
6b	>100	14
6c	>100	25
6d	33	92
7a	72	75
7b	20	100
8a	>100	40
8b	>100	35
8c	10	100
8d	>100	38
10	25	83
11	15	100
14	18.6	71
15	10.4	100
19a	19.7	92
20a + 21a	7.65	100
19b	precipitates	–
20b + 21b	1.13	100
19c	20.5	96
20c + 21c	5	100
19d	50.8	75
IS-5-MN	>100	30
ISDN	2.2	100
NTG	0.1	100
3	21	87
3 + thiazolidine-4-carboxylic acid	21	85

our analyses were calculated for net formulas including fractions of 1 H_2O. – For chromatographic purifications, silica gel of type Kieselgel 60, 230–400 mesh ASTM was used. – The following abbreviations are used: DCC (1,3-dicyclohexylcarbodiimide), CMC [1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate], HOBt (1-hydroxybenzotriazole hydrate), DCU (dicyclohexylurea). Reagents were obtained from Sigma-Aldrich Co. (Saint-Quentin-Fallavier, France).

2-O-[S-(Acetamidomethyl)-N-(tert-butoxycarbonyl)]-L-cysteinyl-5-O-nitro-1,4:3,6-dianhydro-D-glucitol (**5a**): 1,4:3,6-Dianhydro-D-glucitol-5-nitrate (1.91 g, 10 mmol), *S*-acetamidomethyl-*N*-*t*Boc-L-cysteine (3.5 g, 12 mmol), DCC (2.47 g, 12 mmol), HOBt (1.6 g, 12 mmol) and 4-pyrrolidinopyridine (0.2 g, 1.3 mmol) were stirred at room temp. in 100 ml of dry dichloromethane for 6 h. DCU was removed by filtration and the solution was washed successively with 30 ml of 5% aqueous acetic acid, 30 ml of water, 30 ml of sodium bicarbonate solution, and water. Purification by flash chromatography [ethyl acetate/heptane (1:1 then 4:1)] and recrystallization from acetone/diisopropyl ether (1:1) gave 3.4 g (73%) of **5a**, mp 105–106°C, $[\alpha]_D^{20} = +59$ ($c = 0.50$, in acetone). – IR: $\tilde{\nu} = 3343$ cm^{-1}, 1738, 1678, 1645, 1526, 1282, 1100, 847. – ^1H NMR: see Table 4. – $C_{17}H_{27}N_3O_{10}S$ (465): calcd. C 43.87, H 5.85, N 9.03, O 34.37; found C 43.8, H 5.8, N 8.7, O 34.11.

2–O-[S-(Acetamidomethyl)]-L-cysteinyl-5-O-nitro-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**6a**): 2.9 g (6.2 mmol) of **5a** was added to 24 ml of 2 N hydrochloric acid in ethyl acetate (obtained by bubbling gaseous HCl into dry AcOEt and adjusting the value of 2 N by dilution), and the solution was stirred for 5 h at room temp. The precipitate formed was then filtered, washed with ether and recrystallized from ethanol/acetone to give 2.15 g (85%) of **6a**; mp 152–155°C, $[\alpha]_D^{20} = +55$ ($c = 0.6$ in water). – IR: $\tilde{\nu} = 3233$ cm^{-1}, 3058, 2931, 1745, 1636, 1282, 1231, 1190 . – ^1H NMR: see Table 4. – $C_{12}H_{19}N_3O_8S \cdot 0.8\ H_2O$ (365 + 0.8 H_2O): calcd.C 34.62, H 5.22, Cl 8.51, N 10.09, O 33.82; found C 34.7, H 5.23, Cl 8.63, N 9.71, O 34.08.

5-O-[S-(Acetamidomethyl)-N-tert-butoxycarbonyl)]-L-cysteinyl-2-O-nitro-1,4:3,6-dianhydro-D-glucitol (**5b**): 1,4:3,6-Dianhydro-D-glucitol-2-nitrate (**2**) (3.5 g, 18 mmol), *S*-acetamidomethyl-*N*-*t*Boc-L-cysteine (5.3 g, 18 mmol), DCC (3.78 g, 18 mmol), HOBt (2.43 g, 18 mmol) and 4-pyrrolidinopyridine (0.3 g, 2 mmol) were stirred at room temp. in 150 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a** and flash chromatography with ethyl acetate/heptane (4:3 then 9:1), the product was recrystallized from acetone/diisopropyl ether (2:3); 3.95 g (46%) of **5b** was obtained; mp 115°C, $[\alpha]_D^{20} = +11$ ($c = 0.6$ in ethanol). – IR: $\tilde{\nu} = 3358$ cm^{-1}, 1753, 1683, 1645, 1625, 1524, 1294, 1222. – ^1H NMR: see Table 4. – $C_{17}H_{27}N_3O_{10}S$ (465): calcd. C 43.87, H 5.85, N 9.03, found C 43.8, H 5.9, N 9.0.

5–O-[S-(Acetamidomethyl)]-L-cysteinyl-2-O-nitro-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**6b**): 2.3 g (4.9 mmol) of **5b** was added to 21 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 1 h at room temp. A precipitate was then filtered, washed with ether and recrystallized from ethanol. 1.75 g (88%) of **6b** was obtained; mp 161–162°C, $[\alpha]_D^{20} = +31.6$ ($c = 0.6$ in water). – IR: $\tilde{\nu} = 3173$ cm^{-1}, 3054, 2616, 1738, 1641, 1568, 1279, 1094, 860. – ^1H NMR see Table 4. – $C_{12}H_{19}N_3O_8S$ (365): calcd.C 35.86, H 5.01, N 10.45; found C 35.4, H 4.9, N 10.3.

5-N-[S-(Acetamidomethyl)-N-(tert-butoxycarbonyl)]-L-cysteinamidyl-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**5c**): *N*-*t*Boc-*S*-acetamidomethyl-L-cysteine (3.95 g, 13.5 mmol), DCC (2.8 g, 13.5 mmol), and HOBt (1.82 g, 13.5 mmol) were successively added, at room temp, to a stirred solution of 5-amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (2.56 g, 13.5 mmol) in 120 ml of dry dichloromethane. After 24 h, DCU was removed by filtration and the pasty compound purified by flash chromatography (ethyl acetate). After recrystallization from ethyl acetate, 5.9 g (94%) of **5c** was obtained; mp 152°C, $[\alpha]_D^{20} = +26$ ($c = 0.6$ in acetone). – IR: $\tilde{\nu} = 3317$ cm^{-1}, 1715, 1685, 1657, 1632, 1554, 1527, 1274, 1171, 856. – ^1H NMR: see Table 4. – $C_{17}H_{28}N_4O_9S$ (463): calcd. C 43.96, H 6.07, N 12.06; found C 44.1, H 6.0, N 12.0.

5-N-[S-(Acetamidomethyl)]-L-cysteinamidyl-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol Hydrochloride (**6c**): 2 g (4.3 mmol) of **5c** was added to 13 ml of 1.6 N methanolic hydrochloric acid, and the solution was stirred for 24 h at room temp. A white solid was then filtered and the filtrate purified by flash chromatography [ethyl acetate, then ethyl acetate/methanol (4:1 then 7:3)]. The viscous oil was crystallized from pyridine and acetone and recrystallized from ethanol/acetone, then from ethanol to give 0.95 g (55%) of **6c**; mp 183°C, $[\alpha]_D^{20} = +28$ ($c = 0.6$ in water). – IR: $\tilde{\nu} = 3196$ cm^{-1}, 1684, 1628, 1546, 1282, 1095, 859. – ^1H NMR: see Table 4. – $C_{12}H_{20}N_4O_7S \cdot 0.15\ H_2O$ (364 + 0.15 H_2O): calcd. C 35.71, H 5.31, N 13.88; found C 35.7, H 5.3, N 13.7.

2-N-[S-(Acetamidomethyl)-N-(tert-butoxycarbonyl)]-L-cysteinamido-2-deoxy-5-O-nitro-1,4:3,6-dianhydro-D-glucitol (**5d**): *S*-acetamidomethyl-*N*-*t*Boc-L-cysteine (6.4 g, 21.8 mmol), DCC (4.53 g, 21.9 mmol), and HOBt (2.95 g, 21.8 mmol) were succesively added at room temp. to a stirred solution of 2-amino-2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate (4.15 g, 21.8 mmol) in 200 ml of dry dichloromethane. After 24 h, DCU was removed by filtration and the compound purified by flash chromatography [ethyl acetate then

Table 4. ^{1}H-NMR chemical shifts (δ; TMS) of **5*** and **6*** in C_5D_5N (300 MHz)

	NH_2, HCl	NH-Boc	NH-CO	NH-Acm	1-H, 1′-H	2-H	3-H	4-H	5-H	6-H, 6′-H	7-H	8-H, 8′-H	9-H, 9′-H	CH_3	*t*Bu
5a		8.76 1 H, d 8.4 Hz		9.5 1 H, m	4. 16 1 H, d 10.7 Hz 4.06 1 H, m	5.5 2 H, m	4.74 1 H, m	5.21, 1 H, t 5.1 Hz	5.5, 2 H, m	4.06 2 H, m 3.86 1 H, dd 11.4, 5.4 Hz	5.06 1 H, m	3.5 1 H, dd 13.8, 5.7 Hz 3.39 1 H, dd 13.8, 7.8 Hz	4.74 2 H, m	2.08 3 H, s	1.49 9 H, s
5b		8.66 1 H, d 8.4 Hz		9.43 1 H, m	4.33 1 H, dd 11.7, 3.6 Hz 4.22 1 H, d 11.7 Hz	5.56 1 H, d 3.2 Hz	4.7 1 H, d 5.5 Hz	5.03 1 H, t 5.5 Hz	5.4 1 H, m	4.06 1 H, dd 10.4, 3.1 Hz 3.89 1 H, dd 10.4, 5 Hz	5.17 1 H, ddd 8.7, 8.4, 5.3 Hz	3.57 1 H, dd 13.9, 5.3 Hz 3.38 1 H, dd 13.9, 8.7 Hz	4.8 1 H, dd 14, 6.3 Hz 4.73 1 H, m	2.08 3 H, s	1.49 9 H, s
5c		8.45 1 H, d 8.4 Hz	9.09 1 H, d 6.9 Hz	9.5 1 H, m	4.13 1 H, dd 11.4, 4 Hz 4.07 1 H, d 11.4 Hz	5.53 1 H, m	5.01 1 H, d 4.1 Hz	5.06 1 H, d 4.1 Hz	4.72 1 H, m	4.0 1 H, dd 9.6, 4.7 Hz 3.92 1 H, d 9.6 Hz	5.12 1 H, m	3.41 1 H, dd 13.9, 5.2 Hz; 3.19 1 H, dd 13.9, 8.6 Hz	4.93 1 H, dd 13.6, 9.3 Hz 4.4 1 H, dd 13.6, 5.6 Hz	2.03 3 H, s	1.47 9 H, s
5d		8.48 1 H, d 8.7 Hz	9.19 1 H, d 6.4 Hz	9.48 1 H, m	4.05 1 H, d 10.6 Hz 4.0 1 H, m	4.7 1 H, m	4.78 1 H, d 5 Hz	5.12 1 H, t 5 Hz	5.45 1 H, ddd 5.4, 5.2 Hz	4.0 1 H, m 3.83 1 H, dd 11.4, 5.4 Hz	5.08 1 H, m	3.41 1 H, dd 13.7, 6.3 Hz 3.23 1 H, dd 13.7, 7.9 Hz	4.89 1 H, dd 13.4, 7.2 Hz 4.45 1 H, dd 13.4, 5.2 Hz	2.02 3 H, s	1.46 9 H, s
6a	8.11 3 H, m			9.85 1 H, t 6 Hz	4.09 2 H, m	5.53 1 H, m	5.05 1 H, t 5.2 Hz	5.26 1 H, t 5.2 Hz	5.53 1 H, m	4.09 1 H, m 3.89 1 H, dd 11.3, 5.3 Hz	4.88 1 H, m	3.8 2 H, d 5.4 Hz	4.88 1 H, m 4.76 1 H, dd 13.5, 6. Hz	2.12 3 H, s	
6b	9.35 3 H, m			9.92 1 H, m	4.24 1 H, dd 11.5, 3.6 Hz 4.14 1 H, m	5.6 1 H, d 3.4 Hz	4.74 1 H, d 5.2 Hz	5.08 1 H, m	5.5 1 H, m	4.14 1 H, m 3.95 1 H, dd 10.6, 5.1 Hz	5.08 1 H, m	3.84 2 H, m	4.91 1 H, dd 13.5, 6 Hz 4.82 1 H, dd 13.5, 6.3 Hz	2.13 3 H, s	
6c	7.2 3 H, m		10.61 1 H, d 6.5 Hz	10.26 1 H, t 6.3 Hz	4.15 1 H, dd 11.4, 4.15 Hz 4.06 1 H, m	5.53 1 H, d 2.7 Hz	5.17 1 H, d 4.2 Hz	5.28 1 H, d 4.2 Hz	4.73 1 H, m	4.06 2 H,m	5.20 1 H, m	3.97 1 H,dd 14.3, 4.0 Hz 3.39 1 H, dd 14.3, 9.6 Hz	4.82 ; 1 H, dd 13.5, 6.2 Hz 4.72 1 H, dd 13.5, 6.5 Hz	2.15 3 H, s	
6d					3.97 2 H, m	4.36 1 H, d 3.1 Hz	4.51 1 H, d 5 Hz	5.07 1 H, dd 5.2, 5 Hz	5.56 1 H, ddd 5.3, 5.2, 2.2 Hz	4.1 1 H, dd 11.5, 2.2 Hz 3.97 1 H, m	4.18 1 H, dd 7.2, 6.2 Hz	3.09, 1 H dd, 14.3, 6.2 Hz 3.03 1 H, dd 14.3, 7.2 Hz	4.37 1 H, d 14 Hz 4.29 1 H, d 14 Hz	2.0 3 H, s	

ethyl acetate/methanol (95:5)]. After recrystallization from ethyl acetate, 4.5 g (44%) of **5d** was obtained; mp 90−92°C, $[\alpha]_D^{20}$ = +78 (*c* = 0.6 in ethanol). − IR: $\tilde{\nu}$ = 3306 cm^{-1}, 1689, 1657, 1633, 1549, 1509, 1282, 1173, 1088, 858. − ^{1}H NMR: see Table 4. −

$C_{17}H_{28}N_4O_9S \cdot 0.6\ H_2O$ (464 + 0.6 H_2O): calcd. C 42.9, H 6.2, N 11.7, O 32.4; found C 42.96, H 6.18, N 11.78, O 32.31.

2-N-[S-(Acetamidomethyl)]-L-cysteinamido-2-deoxy-5-O-nitro-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**6d**): 4.3 g (9.25 mmol) of **5d** was added to 23 ml of 2.2 N methanolic hydrochloric acid, and the solution was stirred for 18 h at room temp. The solution was concentrated and the residue purified by flash chromatography [ethyl acetate then ethyl acetate/methanol (4:1 then 7:3 and then 3:2)]. After recrystallization from ethanol, 3.1 g (83%) of **6d** was obtained; mp 94−95°C, $[\alpha]_D^{20}$ = +74 (*c* = 0.6 in water). − IR: $\tilde{\nu}$ = 3243 cm^{-1}, 3060, 1690, 1635, 1553, 1486, 1282, 1093, 857. − ^1H NMR: see Table 4. − $C_{12}H_{20}N_4O_7S \cdot 0.8\ H_2O$ (364 + 0.8 H_2O): calcd. C 34.71, H 5.23, Cl 8.53, N 13.49; found C 34.7, H 5.4, Cl 8.6, N 13.3.

2-O-[(3-tert-Butoxycarbonyl-4(R)-thiazolidinyl)carbonyl]-5-O-nitro-1,4:3,6-dianhydro-D-glucitol (**7a**): 1,4:3,6-Dianhydro-D-glucitol-5-nitrate (5 g, 26.1 mmol), *N*-*t*Boc-L-thioproline (6.15 g, 26.3 mmol), DCC (5.4 g, 26.1 mmol), HOBt (3.55 g, 26.2 mmol) and 4-pyrrolidinopyridine (0.435 g, 2.9 mmol) were stirred at room temp. in 225 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a**, recrystallization from ethyl acetate and washing with petroleum ether, 5.5 g (51%) of **7a** was obtained; mp 106−110°C, $[\alpha]_D^{20}$ = +10 (*c* = 0.6 in acetone). − IR: $\tilde{\nu}$ = 1756 cm^{-1}, 1702, 1645, 1391, 1282, 1167, 1101, 854. − ^1H NMR: see Table 5. − $C_{15}H_{22}N_2O_9S$ (406): calcd. C 44.33, H 5.45, N 6.89; found C 44.4, H 5.5, N 6.8.

5-O-Nitro-2-O-{[4(R)-thiazolidinyl]carbonyl}-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**8a**): 2.5 g (6.1 mmol) of **7a** was added to 32 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 1 h at room temp. A precipitate was then filtered, washed with ether and recrystallized from ethanol. 2.85 g (76%) of **8a** was obtained; mp 183°C (dec.), $[\alpha]_D^{20}$ = +42 (*c* = 0.6 in water). − IR: $\tilde{\nu}$ = 1757 cm^{-1}, 1628, 1284, 1226, 1098, 852. − ^1H NMR: see Table 5. − $C_{10}H_{14}N_2O_7S$ (313): calcd. C 35.04, H 4.41, N 8.17; found C 34.7, H 4.4, N 8.1.

5-O-{[3-tert-Butoxycarbonyl-4(R)-thiazolidinyl]carbonyl}-2-O-nitro-1,4:3,6-dianhydro-D-glucitol (**7b**): 1,4:3,6-Dianhydro-D-glucitol-2-nitrate (6 g, 31.4 mmol), *N*-*t*Boc-L-thioproline (7.38 g, 31.6 mmol), DCC (6.48 g, 31.4 mmol), HOBt (4.26 g, 31.5 mmol), and 4-pyrrolidinopyridine (0.52 g, 3.5 mmol) were stirred at room temp. in 270 ml of dry dichloromethane (stabilized with amylene) for 24 h. After the same treatment as desribed for **5a** and recrystallization from ethyl acetate/petroleum ether, 7.6 g (60%) of **7b** was obtained; mp 93°C, $[\alpha]_D^{20}$ = −15 (*c* = 0.6 in ethanol). − IR: $\tilde{\nu}$ = 1765 cm^{-1}, 1697, 1640, 1382, 1367, 1307, 1274, 1194, 1164, 1091, 863. − ^1H NMR: see Table 5. − $C_{15}H_{22}N_2O_9S \cdot 0.15\ H_2O$ (406 + 0.15 H_2O): calcd. C 44.03, H 5.48, N 6.84; found C 44.0, H 5.4, N 6.8.

2-O-Nitro-5-O-{[4(R)-thiazolidinyl]carbonyl}-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**8b**): 6.8 g (16.7 mmol) of **7b** was added to 65 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 1 h at room temp. A precipitate was then filtered, washed with ether and recrystallized from methanol. 2.35 g (40%) of **8b** was obtained; mp 175°C (dec.), $[\alpha]_D^{20}$ = +15 (*c* = 0.6 in water). − IR: $\tilde{\nu}$ = 1761 cm^{-1}, 1635, 1309, 1279, 1250, 1201, 1097, 906, 862. − ^1H NMR: see Table 5. − $C_{10}H_{14}N_2O_7S \cdot 0.15\ H_2O$ (306 + 0.15 H_2O): calcd. C 34.75, H 4.45, N 8.10; found C 34.7, H 4.4, N 7.9.

5-Deoxy-2-O-nitro-5-({[4(R)-thiazolidinyl]carbonyl}amino)-1,4:3,6-dianhydro-L-iditol Hydrochloride (**8c**): *N*-*t*Boc-L-thioproline (6.13 g, 26.3 mmol), DCC (5.43 g, 26.3 mmol) and HOBt (3.55 g, 26.3 mmol) were successively added at room temp. to a stirred solution of 5-amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (5 g, 26.3 mmol) in 300 ml of dry dichloromethane. After 24 h, the same treatment as described for **5a** and flash chromatography [ethyl acetate then ethyl acetate/methanol (9:1)] gave 10.5 g of an oil corresponding to **7c**. This oil did not crystallize and was used immediately in the next step. 10.5 g of **7c** was added to 80 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 3 h at room temp. A precipitate was then filtered, washed with ether and recrystallized from methanol. 7.35 g (81%) of **8c** was obtained; mp 185−195°C (dec.), $[\alpha]_D^{20}$ = −60 (*c* = 2 in water). − IR: $\tilde{\nu}$ = 3271 cm^{-1}, 2932, 1692, 1652, 1553, 1283, 859. − ^1H NMR: see Table 5. − $C_{10}H_{15}N_3O_6S$ (305): calcd. C 35.14, H 4.72, Cl 10.37, N 12.30; found C 35.1, H 4.5, Cl 10.4, N 12.1.

2-Deoxy-5-O-nitro-2-[{[4(R)-thiazolidinyl]carbonyl}amino]-1,4:3,6-dianhydro-D-glucitol Hydrochloride (**8d**): L-Thioproline (3.1 g, 23.3 mmol), DCC (4,8 g, 23.3 mmol), and HOBt (3.15 g, 23.3 mmol) were successively added at room temp. to a stirred solution of 2-amino-2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate (4.45 g, 23.4 mmol) in 200 ml of dry dichloromethane. After 24 h, DCU was removed by filtration and the compound purified by flash chromatography [ethyl acetate then ethyl acetate/methanol (9:1)]. The oily compound was dissolved in dichloromethane and after treatment with dry hydrogen chloride and concentration, the residue was crystallized and recrystallized from methanol to give 2.3 g (29%) of **8d**; mp 187−188°C (dec.), $[\alpha]_D^{20}$ = +11 (*c* = 0.6 in water). − IR: $\tilde{\nu}$ = 3196 cm^{-1}, 3072, 2821, 2702, 2553, 1666, 1569, 1281, 1096, 844. − ^1H NMR: see Table 5. − $C_{10}H_{15}N_3O_6S$ (305): calcd. C 35.14, H 4.72, Cl 10.37, N 12.30, S 9.38; found C 35.2, H 4.7, Cl 10.3, N 11.7; S, 9.2.

5-Deoxy-2-O-nitro-5-[{[3-formyl-2,2-dimethyl-4(R)-thiazolidinyl]carbonyl}amino]-1,4:3,6-dianhydro-L-iditol (**9**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (2.94 g, 15.5 mmol), L-3-formyl-2,2-dimethylthiazolidine-4-carboxylic acid[24] (2.95 g, 15,5 mmol), DCC (3.20 g, 15.5 mmol) and HOBt (2.1 g, 15.5 mmol) were stirred at room temp. in 150 ml of dry dichloromethane for 24 h. DCU was removed by filtration and the solid compound was purified by flash chromatography (ethyl acetate then methanol). After recrystallization from methanol, 3.05 g (54%) of **9** was obtained; mp 158°C, $[\alpha]_D^{20}$ = 59 (*c* = 0.6 in acetone). − IR: $\tilde{\nu}$ = 1688 cm^{-1}, 1646, 1573, 1376, 1361, 1287, 1101, 853. − ^1H NMR: see Table 6. − $C_{13}H_{19}N_3O_7S$ (361): calcd. C 43.20, H 5.30, N 11.63; found C 43.0, H 5.3, N 11.7.

5-Deoxy-5-[{[2,2-dimethyl-4(R)-thiazolidinyl]carbonyl}amino]-2-O-nitro-1,4:3,6-dianhydro-L-iditol Hydrochloride (**10**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (3 g, 15.8 mmol), L-2,2-dimethylthiazolidine-4-carboxylic acid[24] (3.07 g, 15,5 mmol), DCC (3.26 g, 15.7 mmol), and HOBt (2.14 g, 15.7 mmol) were stirred at room temp. in 130 ml of dry dichloromethane for 24 h. DCU was removed by filtration and the oily compound was purified by flash chromatography (ethyl acetate) then dissolved in dichloromethane and dry hydrogen chloride was slowly bubbled into the solution. After concentration, the residue was crystallized and recrystallized from methanol to give 2.7g (47%) of **10**; mp 196°C (dec.), $[\alpha]_D^{20}$ = −12 to +17 (*c* = 0.6 in water) (variation in 1 h due to instability of this compound in water). − IR: $\tilde{\nu}$ = 3055 cm^{-1}, 1693, 1634, 1562, 1281, 1098, 856. − ^1H NMR: see Table 6. − $C_{12}H_{19}N_3O_6S$ (333): calcd. C 38.78, H 5.43, Cl 10.01, N 11.30, O 25.82, S 8.62; found C 38.51, H 5.43, Cl 9.92, N 11.12, O 25.48, S 9.16.

5-[{[3-Acetyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**14**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (2 g, 10.5 mmol), 3-acetyl-thiazolidine-

Table 5. ^{1}H-NMR chemical shifts (δ; TMS) of **7**[a] and **8**[a] in C_5D_5N (300 MHz)

	NH,HCl	NH	1-H,1′-H	2-H	3-H	4-H	5-H	6-H,6′-H	7-H	8-H	9-H	*t*Bu
7a			4.12 2 H, m	5.54 1 H, m	4.57−4.7 1 H, m	5.18 1 H, m	5.51 1 H, m	4.1 1 H, m 3.90 1 H, m	5.09 1 H, m	3.30 2 H, m	4.57−4.7 2 H, m	1.47 9 H, s
7b			4.26 2 H, m	5.61 1 H, m	4.72 1 H, m	5.05 1 H, m	5.41 1 H, m	3.98 2 H, m	5.05 1 H, m	3.38 2 H, m	4.72 2 H, m	1.51 9 H, s
8a	8.8 2 H, m		4.15 1 H, d 10.8 Hz 4.07 1 H, m	5.46 1 H, d 2.6 Hz	4.62 1 H, d 4.9 Hz	5.17 1 H, dd 5.3, 4.9 Hz	5.54 1 H, ddd 5.54, 5.3, 2.2 Hz	4.07 1 H, m 3.92 1 H, dd, 11.3, 5.4 Hz	4.2 1 H, dd 7, 6.4 Hz	3.22 1 H, dd 10.2, 7 Hz 3.09 1 H, dd 10.2, 6.4 Hz	4.51 1 H, d 9 Hz 4.29 1 H, d 9 Hz	
8b	11.08 2 H, s		4.23 2 H, m	5.59 1 H, d 3 Hz	4.76 1 H, d 5.3 Hz	5.09 1 H, dd 5.5, 5.3 Hz	5.43 1 H, ddd 5.5, 5.1, 3.7 Hz	4.04 1 H, dd 10.4, 3.7 Hz 3.95 1 H, dd 10.4, 5.1 Hz	4.35 1 H, dd 7.1, 6.4 Hz	3.31 1 H, dd 10.1, 7.1 Hz 3.21 1 H, dd 10.1, 6.4 Hz	4.56 1 H, d 9.1 Hz 4.34 1 H, d 9.1 Hz	
8c	9.5 2 H, m	9.1 1 H, m	4.15 1 H, dd 11.45, 4.1 Hz 4.08 1 H, dd 11.45, 1.6 Hz	5.52 1 H, dd 4.1, 1.6 Hz	4.9 1 H, m	4.9 1 H, m	4.72 1 H, m	4.07 1 H, dd 9.5, 5 Hz 3.98 1 H, dd 9.5, 2.5 Hz	4.31 1 H, dd 7, 5.6 Hz	3.52 1 H, dd 10,5, 6 Hz 3.22 1 H, dd 10, 7 Hz	4.32 1 H, d 9.3 Hz 4.27 1 H, d 9.3 Hz	
8d	11.03 2 H, s	9.27 1 H, d 6.8 Hz	4.09 2 H, m	4.73 1 H, m	4.76 1 H, d 5 Hz	5.19 1 H, dd 5.3, 5 Hz	5.49 1 H, dt 5.3, 5.3, 2 Hz	4.07 1 H, dd 11.4, 2 Hz 3.88 1 H, dd 11.4, 5.3 Hz	4.41 1 H, dd 7, 6.1 Hz	3.47 1 H, dd 10.1, 6.1 Hz 3.34 1 H, dd 10.1, 7 Hz	4.39 1 H, d 9.4 Hz 4.29 1 H, d 9.3 Hz	

[a] See numbering for each compound in Table 1.

4(*R*)-carboxylic acid[25] (1.84 g, 10.5 mmol), CMC (4.45 g, 10.5 mmol), and HOBt (1.42 g, 10.5 mmol) were stirred at room temp. in 80 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a**, the solid compound was recrystallized from ethyl acetate to give 1.6 g (44%) of **14**; mp 169°C. Two conformers are detected by ^{1}H NMR [**A** (75%) and **B** (25%)], $[\alpha]_D^{20} = -62$ (c = 1 in ethanol). − IR: $\tilde{\nu}$ = 3269 cm^{-1}, 1688, 1641, 1563, 1446, 1417, 1287, 1275, 1238, 1100, 850. − ^{1}H NMR: see Table 6. − $C_{12}H_{17}N_3O_7S$ (347): calcd. C 41.50, H,4.93, N 12.10; found C 41.4, H 4.9, N 12.1.

5-[{[3-Benzoyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**15**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (2 g, 10.5 mmol), 3-benzoyl-thiazolidine-4(*R*)-carboxylic acid[26] (2.5 g, 10.5 mmol), DCC (2.16 g, 10.5 mmol), and HOBt (1.42 g, 10.5 mmol) were stirred at room temp. in 100 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a**, the solid compound was recrystallized from methanol to give 2.04 g (40%) of **15**; mp 166−167°C, $[\alpha]_D^{20} = -106$ (c = 1 in DMSO). − IR: $\tilde{\nu}$ = 3296 cm^{-1}, 1689, 1631, 1275, 853. − ^{1}H NMR: see Table 6. − $C_{17}H_{19}N_3O_7S$ (409): calcd. C 49.87, H 4.68, N 10.26; found C 49.7, H 4.6, N 10.2.

2(RS)-Methylthiazolidine-4(R)-carboxylic Acid **16a** + **17a**: These compounds were synthesized according to the procedure described by Nagasawa et al.[16]. − IR: $\tilde{\nu}$ = 3046 cm^{-1}, 1614, 1391, 1367.

N-tert-Butoxycarbonyl-2(R)-methylthiazolidine-4(R)-carboxylic Acid (**18a**): This compound was synthesized according to the procedure described by Kleemann et al.[33] from **16a** + **17a** and was obtained in 76% yield; mp 118−119°C, $[\alpha]_D^{20} = -67$ (c = 1.0 in methanol). − IR: $\tilde{\nu}$ = 2976 cm^{-1}, 1729, 1621, 1428, 1169.

2(RS)-Phenylthiazolidine-4(R)-carboxylic Acid (**16b** + **17b**): These compounds were synthesized according to the procedure described by Paul et al.[18]. − IR: $\tilde{\nu}$ = 1576 cm^{-1}, 1436, 1382, 1306, 858.

N-tert-Butoxycarbonyl-2(R)-phenylthiazolidine-4(R)-carboxylic Acid (**18b**): This compound was synthesized according to the procedure described by Kleemann et al.[27] from **16b** + **17b** and was obtained in 89% yield; mp 172−173°C, $[\alpha]_D^{20} = +91$ (c = 1.0 in methanol). − IR: $\tilde{\nu}$ = 1726 cm^{-1}, 1632, 1420, 1368, 1350, 1328, 1290, 1248, 1172, 1138.

Table 6. ^{1}H-NMR chemical shifts (δ; TMS) of **9**[a], **10**[a], **14**[a], and **15**[a] in C_5D_5N (300 MHz)

	NH	CHO	H_{arom}	1-H, 1′-H	2-H	3-H	4-H	5-H	6-H, 6′-H	7-H	8-H, 8′-H	9-H, 9′-H	CH_{3gem}	CH_3-CO
9	9.36 1 H, d 6.8 Hz	8.69 1 H, s		4.12 1 H, dd 11.5, 4 Hz 4.01 1 H, m	5.48 1 H, m	4.85 1 H, d 4.3 Hz	4.94 1 H, d 4.3 Hz	4.72 1 H, m	4.01 2 H, m	5.3 1 H, dd 7.4, 5.6 Hz	3.53 1 H, dd 12, 5.6 Hz 3.4 1 H,dd 12, 7.4 Hz		1.93 3 H, s 1.75 3 H, s	
10	9.21 1 H, d 6.7 Hz			4.17 1 H, dd 11.4; 4 Hz 4.09 1 H, m	5.54 1 H, m	4.92 1 H, d 4.2 Hz	4.96 1 H, d 4.2 Hz	4.77 1 H, m	4.09 1 H,m 3.99 1 H,dd 9.5; 1.9 Hz	4.34 1 H, t 7.6 Hz	3.49 2 H, m		1.65 3 H, s 1.53 3 H, s	
14	9.49 d/B 6.1 Hz 9.31 d/A 6.1 Hz			3.9−4.2 2 H, m	5.50 m, B 5.47 m, A	4.83 1 H, d 4 Hz	4.95 1 H, d 4 Hz	5.01 m,A 4.86 m,B	3.9−4.2 2 H, m	5.27 dd, A 7.2, 4.7 Hz 4.98 m, B	3.65 dd,B 11.6, 3.6 Hz 3.48 dd,A 11.6, 4.7 Hz 3.44 m,B 3.31 dd, A 11.6, 7.2 Hz	4.68 2 H, m		2.17 B, s 2.03 A, s
15	9.13 1 H, d 6 Hz		7.65 2 H, m 7.36 3 H, m	4.11 1 H, dd 11.4, 4.3 Hz 3.99 1 H, dd 11.4, 1.8 Hz	5.44 5.44 1 H, m	4.78 1 H, d 4.2 Hz	4.90 1 H, d 4.2 Hz	4.67 1 H, m	4.03 1 H, dd 9.6, 5.1 Hz 3.92 1 H, dd 9.6, 2.2 Hz	5.37 1 H, m	3.5 1 H, dd 11.5, 5.8 Hz 3.41 1 H, dd 11.5, 7.4 Hz	4.84 2 H, m		

[a] See numbering for each compound in Table 1.

2(RS)-n-Butylthiazolidine-4(R)-carboxylic Acid (**16c** + **17c**): These compounds were synthesized according to the procedure described by Paul et al.[18]. − IR: $\tilde{\nu}$ = 2956 cm^{-1}, 2748, 1582, 1381, 1297, 1140, 846, 817, 617.

N-tert-Butoxycarbonyl-2(R)-n-butylthiazolidine-4(R)-carboxylic Acid (**18c**): This compound was synthesized according to the procedure described by Kleemann et al.[27] from **16c** + **17c** and was obtained in 93% yield. Oil. − IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2933, 1703, 1370, 1169, 1145. − Two conformers of **18c** (**A** and **B**) were detected by ^{1}H NMR.

Thiazolidine-2(R),4(R)-dicarboxylic Acid 2-Methyl Ester (**16d**): This compound was synthesized according to the procedure described by Baxter et al.[20]. − IR: $\tilde{\nu}$ = 3040 cm^{-1}, 1752, 1741, 1625, 1476, 1441, 1377, 1311, 1279, 1241, 1221, 1174, 1012.

N-tert-Butoxycarbonylthiazolidine-2(R),4(R)-dicarboxylic Acid 2-Methyl Ester (**18d**): This compound was synthesized according to the procedure described by Kleemann et al.[27] from **16d** and was obtained in 70% yield; mp 77−78°C. Two conformers were detected by ^{1}H NMR [**A** (83%) and **B** (17%)]. − IR: $\tilde{\nu}$ = 3530 cm^{-1}, 1747, 1662, 1412, 1370, 1342, 1283, 1211, 1153, 1017. − ^{1}H NMR: see Table 7.

5-[[(3-tert-Butoxycarbonyl-2(R)-methyl-4(R)-thiazolidinyl)carbonyl]amino}-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**19a**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (3 g, 15.7 mmol), *N-tert*-butoxycarbonyl-2(*R*)-methylthiazolidine-4(*R*)-carboxylic acid (**18a**) (3.9 g, 15.7 mmol), DCC (3.26 g, 15.7 mmol), and HOBt (2.13 g, 15.7 mmol) were stirred at room temp. in 120 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a** and flash chromatography [ethyl acetate/heptane (2:3 then 1:1)], the solid compound was recrystallized from ethyl acetate to give 4.17 g (63%) of **19a**; mp 129−130°C, $[\alpha]_D^{20}$ = −18 (*c* = 1.0 in ethanol). − IR: $\tilde{\nu}$ = 3298 cm^{-1}, 1704, 1667, 1646, 1546, 1405, 1274, 1097, 1083, 839. − ^{1}H NMR: see Table 8. − $C_{16}H_{25}N_3O_8S$ (419): calcd. C 45.82, H 6.01, N10.02; found C 45.7, H 6.0, N 10.0.

5-[{[2(RS)-Methyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol Hydrochloride [**20a** (2*R*,4*R*), **21a** (2*S*,4*R*)]: 4.09 g (9.75 mmol) of **19a** was added to 34 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 16 h at room temp. A precipitate was then filtered and washed with ether. After recrystallization from methanol, 2.58 g (74%) of **20a** and **21a** was obtained; mp 209°C (dec.). − $[\alpha]_D^{20}$ = −55 (*c* = 1.0 in water). − IR: $\tilde{\nu}$ = 3230 cm^{-1}, 2884, 2642, 2546, 2498, 1688, 1616, 1562, 1396, 1324, 1282, 1206, 1088, 1038, 956, 892, 862. − ^{1}H NMR (300 MHz, C_5D_5N) (time t_0: 25% **20a**, 75% **21a**; time t_0 + 15 min: 50% **20a**, 50% **21a**): δ = 11.13 (s, 2 H, NH·HCl), 9.77 (d, 0.5 H, *J* = 6.6 Hz, NH **20a**), 9.08 (d, 0.5 H, *J* = 6.8 Hz, NH **21a**), 5.53 (m, 1 H, 2-H), 5.07 (m, 1 H, 3-H or 4-H), 5.0 (m, 1 H, 3-H or 4-H), 4.87 (q, 0.5 H, *J* = 6.2 Hz, 9-H

Table 7. ^{1}H-NMR chemical shifts (δ; TMS) of **18*** in [D_6]DMSO (300 MHz)[a]

	H_{arom}	2-H	4-H	5-H, 5′-H	CH_2	CH_3	*t*Bu
18a		5.12, 1 H, q 6.2 Hz	4.61, 1 H, dd 7.3, 6.2 Hz	3.37, 1 H, dd 11.6, 7.3 Hz 3.22, 1 H, dd 11.6, 6.2 Hz		1.51, 3 H, d 6.2 Hz	1.42, 9 H, s
18b	7.61−7.64, 2 H, m 7.23−7.33, 3 H, m	6.05, 1 H, s	4.71, 1 H, dd 6.8, 6.2 Hz	3.45, 1 H, dd 11.8, 6.8 Hz 3.17, 1 H, dd 11.85, 6.2 Hz			1.27, 9 H, s
18c[b]		5.41, m A 5.29, m B	5.32, m A 5.03, dd B 7.4, 6.8 Hz	3.55, 2 H, m	2.32, 2 H, m 1.97, 2 H, m 1.29, 2 H, m	0.87, 3 H, A 7 Hz 0.79, 3 H, B	1.52, 9 H, m
18d[c]		5.37, s A 5.22, s B	4.55, 1 H, m	3.47, 1 H, m 3.26, 1 H, m		3.66, 3 H, s	1.36, 9 H, s

[a] See numbering for each compound in Table 1. − [b] Spectrum in C_5D_5N. − [c] Spectrum at 200 MHz.

21a), 4.76 (q, 0.5 H, *J* = 6.2 Hz, 9-H **20a**), 4.75 (m, 1 H, 5-H), 4.71 (dd, 0.5 H, *J* = 7.3 and 4.5 Hz, 7-H **21a**), 4.36 (dd, 0.5 H, *J* = 8.7 and 6.9 Hz, 7-H **20a**), 4.04−4.20 (m, 4 H, 1-H and 6-H), 3.74 (dd, 0.5 H, *J* = 10.4 and 4.5 Hz, 8-H **21a**), 3.59 (dd, 0.5 H, *J* = 10 and 6.9 Hz, 8-H **20a**), 3.46 (dd, 0.5 H, *J* = 10.4 and 7.3 Hz, 8-H **21a**), 3.35 (dd, 0.5 H, *J* = 10 and 8.7 Hz, 8-H **20a**), 1.57 (d, 1.5 H, *J* = 6.2 Hz, CH_3 **20a**), 1.51 (d, 1.5 H, *J* = 6.2 Hz, CH_3 **20a**), 1.51 (d, 1.5 H, *J* = 6.2 Hz, CH_3 **21a**). − $C_{11}H_{17}N_3O_6S$ (319): calcd. C 37.13, H 5.10, Cl 9.96, N 11.81; found C 37.2, H 5.1, Cl 9.9, N 11.8.

5-[{[3-tert-Butoxycarbonyl-2(R)-phenyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**19b**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (5 g, 26.29

Table 8. ^{1}H-NMR chemical shifts (δ; TMS) of **19*** in C_5D_5N (300 MHz) at 60°C[a]

	NH	H_{arom}	1-H, 1′-H	2-H	3-H	4-H	5-H	6-H, 6′-H	7-H	8-H, 8′-H	9-H	CH_2	CH_3	*t*Bu
19a	8.7 1 H, d 6.4 Hz		4.14 1 H, dd 11.4, 4.4 Hz 4.01 1 H, m	5.47 1 H, m	4.82 1 H, d 4.25 Hz	4.9 1 H, d 4.25 Hz	4.67 1 H, m	4.08 1 H, dd 9.5, 5 Hz 4.01 1 H, m	4.89 1 H, dd 7.4, 7.3 Hz	3.56 1 H, dd 11.7, 7.4 Hz 3.3, 1 H, dd, 11.7, 7.3 Hz	5.3 1 H, q 6.3 Hz		1.75 3 H, d 6.3 Hz	1.46 9 H, s
19b	8.75 1 H, d 5.2 Hz	7.97 2 H, d 7.5 Hz 7.37 2 H, t 7.5 Hz 7.24 1 H, t 7.5 Hz	4.14 1 H, dd 11.4, 4.4 Hz 4.01 1 H, m	5.47 1 H, m	4.89 1 H, d 4 Hz or 4.81 1 H, d 4 Hz	4.81 1 H, d 4 Hz or 4.89 1 H, d 4 Hz	4.72 1 H, m	4.08 1 H, dd 9.6, 4.8 Hz 4.01 1 H, m	5.01 1 H, dd 7.0, 6.5 Hz	3.59 1 H, dd 11.7, 7 Hz 3. 33 1 H, dd 11.7, 6.5 Hz	6.31 1 H, s			1.33 9 H, s
19c	8.73 1 H, d 6.5 Hz		4.13 1 H, dd 11.4, 4.4 Hz 4.02 1 H, m	5.4 1 H, d 3.2 Hz	4.89 1 H, d 4 Hz or 4.82 1 H, d 4 Hz	4.82 1 H, d 4 Hz or 4.89 1 H, d 4 Hz	4.68 1 H, m	4.08 1 H, dd 9.6, 5.1 Hz 4.02 1 H, m	4.91 1 H, dd 8.1, 7.5 Hz	3.58 1 H, dd 11.7, 8.1 Hz 3.32 1 H, dd 11.7, 7.5 Hz	5.28 1 H, dd 8.6, 5.6 Hz	2.28, 1 H, m (10-H) 1.96, 1 H, m (10-H) 1.29−1.53 4 H, m (11-H, 12-H)	0.87 3 H, m	1.49 9 H, s
19d[b]	8.4 1 H, d 6.2 Hz		4.10 1 H, dd 11.5, 4.3 Hz 4.00 1 H, d 11.5 Hz	5.46 1 H, m	4.64 1 H, m or 4.47 1 H, m	4.47 1 H, m or 4.64 1 H, m	4.22 1 H, m	3.98 1 H, dd 9.6, 4.85 Hz 3.73 1 H, dd 9.6, 2.3 Hz	4.54 1 H, dd 7.1, 5.9 Hz	3.51 1 H, dd 11.8, 7.1 Hz 3.20 1 H, dd 11.8, 5.9 Hz	5.49 1 H, s		3.79 3 H, s	1.39 9 H, s

[a] See numbering for each compound in Table 1. − [b] Spectrum in [D_6]DMSO at 60°C.

mmol), *N-tert*-butoxycarbonyl-2(*R*)-phenylthiazolidine-4(*R*)-carboxylic acid (**18b**) (8.1 g, 26.29 mmol), DCC (5.4 g, 26.29 mmol), and HOBt (3.6 g, 26.29 mmol) were stirred at room temp. in 200 ml of dry dichloromethane for 24 h. After the same treatment as for **5a**, the solid compound was recrystallized from ethyl acetate to give 9.3 g (73%) of **19b**; mp 115°C, $[\alpha]_D^{20} = +87$ ($c = 1.0$ in ethanol). − IR: $\tilde{\nu} = 3346\ cm^{-1}$, 1702, 1636, 1544, 1394, 1368, 1284, 1266, 1250, 1164, 1060, 844. − ^1H NMR: see Table 8. − $C_{21}H_{27}N_3O_8S \cdot 0.5\ H_2O$ (490): calcd. C 51.42, H 5.74, N 8.56; found C 51.3, H 5.6, N 8.6.

5-Deoxy-2-O-nitro-5-[{[2(RS)-phenyl-4(R)-thiazolidinyl]carbonyl}amino]-1,4:3,6-dianhydro-L-iditol Hydrochloride [**20b** (2*R*,4*R*), **21b** (2*S*,4*R*)]: 2 g (4.15 mmol) of **19b** was added to 15 ml of 2 N hydrochloric acid in ethyl acetate, and the solution was stirred for 16 h at room temp. A precipitate (1.65 g) was then filtered and washed with ether. After recrystallization from methanol, 0.95 g (50%) of **20b** and **21b** was obtained; mp 197°C (dec.), $[\alpha]_D^{20} = -38$ ($c = 1.0$ in DMSO). − IR: $\tilde{\nu} = 2886\ cm^{-1}$, 1692, 1626, 1562, 1286, 882. − ^{1}H-NMR (300 MHz, C_5D_5N) (50% **20b**, 50% **21b**): δ = 10.04 (s, 2 H, NH·HCl), 9.62 (d, 0.5 H, $J = 6.7$ Hz, NH **20b**), 9.05 (d, 0.5 H, $J = 6.9$ Hz, NH **21b**), 7.62−7.69 (m, 2 H, Ar), 7.32−7.36 (m, 3 H, Ar), 5.96 (s, 0.5 H, 9-H **21b**), 5.8 (s, 0.5 H, 9-H **20b**), 5.53 (m, 1 H, 2-H), 4.93−5.04 (m, 2 H, 3-H and 4-H), 4.76 (m, 1 H, 5-H), 4.66 (dd, 0.5 H, $J = 7.1$ and 4.85 Hz, 7-H **21b**), 4.37 (dd, 0.5 H, $J = 8.25$ and 7 Hz, 7-H **20b**), 3.95−4.2 (m, 4 H, 1-H and 6-H), 3.83 (dd, 0.5 H, $J = 10.15$ and 4.85 Hz, 8-H **21b**), 3.62 (dd, 0.5 H, $J = 10$ and 7 Hz, 8-H **20b**), 3.52 (dd, 0.5 H, $J = 10$ and 8.25 Hz, 8-H **20b**), 3.49 (dd, 0.5 H, $J = 10.15$ and 7.1 Hz, 8-H **21b**). − $C_{16}H_{19}N_3O_6S \cdot 0.6\ H_2O$ (381 + 0.6 H_2O): calcd. C 44.83, H 4.98, Cl 8.27, N 9.80; found C 44.5, H 4.7, Cl 8.4, N 9.6.

5-[{[3-tert-Butoxycarbonyl-2(R)-butyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**19c**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (4 g, 21 mmol), *N-tert*-butoxycarbonyl-2(*R*)-*n*-Butylthiazolidine-4(*R*)-carboxylic acid (**18c**) (6.08 g, 21 mmol), DCC (4.34 g, 21 mmol), and HOBt (2.84 g, 21 mmol) were stirred at room temp. in 100 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a** and flash chromatography [ethyl acetate/heptane (3:7 then 1:1)], the solid compound (7.8 g) was recrystallized from ethyl acetate/petroleum ether to give 4.76 g (49%) of **19c**; mp 91−92°C, $[\alpha]_D^{20} = +4$ ($c = 1.0$ in ethanol). − IR: $\tilde{\nu} = 3324\ cm^{-1}$, 1670, 1640, 1392, 1276, 1164, 1096, 856. − ^{1}H NMR: see Table 8. − $C_{19}H_{31}N_3O_8S$ (461): calcd. C 49.44, H 6.77, N 9.11; found C 49.7, H 6.7, N 9.1.

5-[{[2(RS)-Butyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol Hydrochloride [**20c** (2*R*,4*R*), **21c** (2*S*,4*R*)]: 3.8 g (8.2 mmol) of **19c** was added to 28 ml of 2 N hydrochloric acid in ethyl acetate and the solution was stirred for 16 h at room temp. A precipitate was then filtered and washed with ether. After recrystallization from methanol, 2.33 g (71%) of **20c** and **21c** was obtained; mp 198−200°C (dec.), $[\alpha]_D^{20} = -34$ ($c = 1.0$ in DMSO). − IR: $\tilde{\nu} = 3240\ cm^{-1}$, 2960, 2886, 1692, 1622, 1568, 1326, 1284, 1090, 1038, 960, 888, 862. − ^{1}H NMR (200 MHz, C_5D_5N) (33% **20c**, 66% **21c**): δ = 9.6 (d, 0.33 H, $J = 6.9$ Hz, NH **20c**), 8.92 (d, 0.66 H, $J = 7$ Hz, NH **21c**), 8.07 (s, 2 H, NH·HCl), 5.53 (m, 1 H, 2-H), 4.97 (m, 2 H, 3-H and 4-H), 4.69 (m, 2.33 H, 9-H, 5-H, and 7-H **20c**), 4.54 (dd, 0.66 H, $J = 7.2$ and 4.5 Hz, 7-H **21c**), 4.01−4.21 (m, 4 H, 1-H and 6-H), 3.73 (dd, 0.66 H, $J = 10.25$ and 4.5 Hz, 8-H **21c**), 3.46 (dd, 0.33 H, $J = 9.9$ and 6.8 Hz, 8-H **20c**), 3.29 (dd, 0.66 H, $J = 10.25$ and 7.2 Hz, 8-H **21c**), 3.28 (dd, 0.33 H, $J = 9.9$ and 8 Hz, 8-H **20c**), 1.59−2.05 (m, 2 H, CH_2 *n*Bu), 1.09−1.44 (m, 4 H, CH_2 *n*Bu), 0.76 (m, 3 H, CH_3). − $C_{14}H_{23}N_3O_6S$ (361): calcd. C 42.31, H 6.09, N 10.58, Cl 8.81; found C 42.1, H 6.0, N 10.4, Cl 8.6.

5-[{[3-tert-Butoxycarbonyl-2(R)-methoxycarbonyl-4(R)-thiazolidinyl]carbonyl}amino]-5-deoxy-2-O-nitro-1,4:3,6-dianhydro-L-iditol (**19d**): 5-Amino-5-deoxy-1,4:3,6-dianhydro-L-iditol-2-nitrate (1.73 g, 9.1 mmol), *N-tert*-butoxycarbonylthiazolidine-2(*R*),4(*R*)-dicarboxylic acid 2-methyl ester (**18d**) (2.66 g, 9.1 mmol), DCC (1.89 g, 9.1 mmol), and HOBt (1.23 g, 9.1 mmol) were stirred at room temp. in 50 ml of dry dichloromethane for 24 h. After the same treatment as described for **5a** and flash chromatography [ethyl acetate/heptane (1:1)], the solid compound (2.45 g) was recrystallized from methanol to give 2.04 g (48%) of **19d**; mp 132−133°C, $[\alpha]_D^{20} = -13$ ($c = 1$ in ethanol). − IR: $\tilde{\nu} = 3295\ cm^{-1}$, 2974, 2883, 1738, 1700, 1688, 1634, 1547, 1482, 1365, 1275, 855. − ^{1}H NMR: see Table 8. − $C_{17}H_{25}N_3O_{10}S$ (531): calcd. C 44.06, H 5.44, N 9.07; found C 44.2, H 5.6, N 9.2.

Pharmacology

Relaxation of Isolated Rat Aortas without Endothelium and Precontracted with Norepinephrin[28]: All experiments were made in accordance with the French Ministry of Agriculture (approval no. 94148). Male Wistar rats (250−350 g) were anesthetized with sodium pentobarbital (60 mg/kg, i.p.), the thoracic aorta was rapidly removed and placed in ice-cold Krebs-Ringer solution of following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, EDTA 0.016, glucose 11. The aorta was cleaned of adhering tissues and cut into ring segments of 3 mm length. Endothelium was mechanically removed by gently rubbing the intimal layer with a forceps. Each segment was mounted in 20 ml organ chambers in Krebs-Ringer solution at 37°C gassed with a mixture of 95% O_2/5% CO_2 for recording of isometric tension. Rings were mechanically stretched to a passive resting tension of 2 g, and allowed to equilibrate for 30 min. The absence of functional endothelium was verified by the inability to relax in response to 1 μM acetylcholine (Sigma, Saint-Quentin-Fallavier, France) following contraction with 0.1 μM norepinephrin (Sigma, Saint-Quentin-Fallavier, France). The rings were then washed three times, allowed to reequilibrate for 30−45 minutes, and constricted again with 0.1 μM norepinephrin. When the maximum of contraction was obtained, the different compounds were added in a cumulative way, with a range of concentration of 1 nM to 100 μM with semi-log increments. Compounds were dissolved in saline when possible, otherwise in ethanol or dimethyl sulfoxide for the stock solution and then diluted in saline. At the end of the experiment, the relaxation obtained with the highest concentration (100 μM) was calculated and referred as maximal relaxation. IC_{50} values (concentration giving 50% of relaxation) were calculated for each compound. Results are the mean of 2 or 3 values obtained from different rats (the different tests performed were screening tests; for this reason, each compound was tested in vitro on 2 or 3 different animals. Furthermore, variations between animals for each compound were very small. The goal of these in vitro tests was to select the compounds with the strongest activity (relaxation > 80% and IC_{50} < 20 μM) for further experimentation in vivo. Therefore we considered that statistic analyses were not very useful in this study and standard deviations were not calculated).

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