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Synthesis and biological evaluation of ureido and thioureido derivatives of 2-amino-2-deoxy-D-glucose and related aminoalcohols as *N*-acetyl-β-D-hexosaminidase inhibitors

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Abstract

Ureido and thioureido derivatives of 2-acetamido-2-deoxy-β-D-glucose, 1-amino-1-deoxy-D-glucitol and 2-(2-aminoethoxy)ethanol were prepared as *N*-acetyl-β-D-hexosaminidase (NAHase) inhibitors and were evaluated on *Trichomonas vaginalis* NAHase. Although none showed complete inhibition of the enzyme at 100 μM, 1-amino-1-deoxy-D-glucitol derivatives acted as competitive inhibitors of the NAHase of *T. vaginalis*.

Keywords: Trichomonas vaginalis; Hexosaminidase inhibitors; 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose; 1-Amino-1-deoxy-D-glucitol; 2-(2-Aminoethoxy)ethanol; Ureido and thioureido derivatives

1. Introduction

N-Acetyl-β-D-hexosaminidases (NAHases) are lysosomal hydrolases of considerable importance in biological systems. They promote the cleavage of *N*-acetyl-β-D-hexosaminides during glycoprotein processing and glycolipid catabolism [1]. NAHase activity has recently been described in *Trichomonas vaginalis* [2], but the role of this enzyme remains unknown. Thus, it is of interest to inhibit NAHase activity in order to assess whether NAHase is implied in *T. vaginalis* development and cytopathic effect. In this respect, NAHase inhibitors could be used as tools to study *T. vaginalis* metabolism and parasite–host interactions. Furthermore, such NAHase inhibitors could be a rationale for the development of new drugs in trichomonasis.

Inhibitors of various NAHases (from plants, bovines, human sources) have already been reported [3]. Some of them were designed for mechanistic investigations [4]. The configuration-retaining aspect of certain NAHases was attributed to the participation of the C-2 acetamido group, initially leading to a cyclised oxazoline intermediate which resembles to the cyclic isourea functionality of allosamidine [5], a natural potent inhibitor from insect chitinase. Therefore, the synthesis of derivatives involving a simple modification of the ac-

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etamido group was of interest. We now report the synthesis of ureido and thioureido derivatives from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose and also from 1-amino-1-deoxy-D-glucitol, which holds a structural analogy with the open form of 2-amino-2-deoxy-β-D-glucose. Further structural analogy between the oxyethylene monohydroxylated chain of 2-aminoethoxyethanol and the glucopyranose hemiacetal functionality led us to synthesize corresponding derivatives from 2-amino-2-ethoxyethanol. These compounds were evaluated on *T. vaginalis* NAHase.

2. Results and discussion

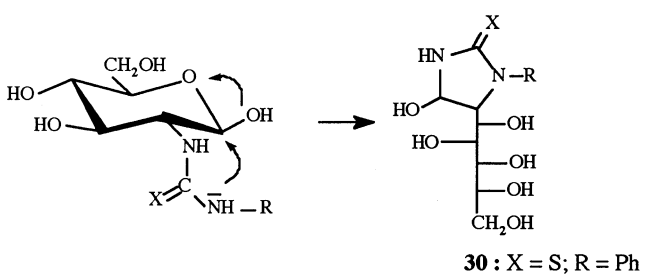
Isothiocyanates **1**–**6**, isocyanates **7**–**10** and diisocyanatoalkanes **11**–**14** were commercially available; diisothiocyanatoalkanes **15**–**21** were synthesized from the primary diamine precursor by a method adapted from Hodgkins et al. and Thorn et al. [6] involving the successive action of carbon disulfide and ethyl chloroformate to give carbethoxydithiocarbamates, followed by base or thermal conversion into isothiocyanates. Since conversion of dithiocarbamates into diisothiocyanates could also be achieved with acid, we found it more convenient to treat the crude chloroform extract containing the dithiocarbamate derivatives with 3 N hydrochloric acid and thus, we improved the yields in diisothiocyanates. Yields of 13–56% were nevertheless obtained for **15**–**21** after chromatographic purification because the reaction also results in monoisothiocyanate with a carbamate functionality as a side product as described previously [6].

The appropriate isothiocyanate or isocyanate was then directly reacted with the amino group of the conveniently protected 2-amino-2-deoxysugar or aminoalcohol at room temperature to give a thiourea or urea derivative, respectively.

Ureido and thioureido derivatives **22**–**29** could be synthesized from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose [7]. The β-(D) anomeric configuration of these compounds was evidenced by the $J_{1,2}$ values (about 8.4 Hz) in the ^{1}H NMR spectra. The non-acetylated analogues of **22**–**29** could not be obtained because they cyclised invariably to 5-hydroxyimidazolidin-2-one or hydroxyimidazolidin-2-thione (Scheme 1) by an intramolecular nucleophilic addition of an NH group to the aldehyde functionality of the sugar, as previously reported by Avalos et al. [8].

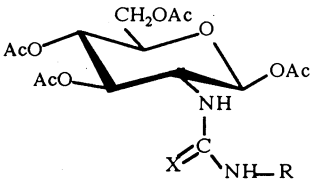
Ureido or thioureido derivatives **31**–**50** and **51**–**71** (Scheme 2) were, respectively, obtained from 1-amino-1-deoxy-D-glucitol and 2-(2-aminoethoxy)ethanol without subsequent cyclization between hydroxyl group and urea or thiourea moiety. ^{1}H NMR spectra of compounds **31**–**39** gave a clear indication of the presence of five hydroxyl groups, the related ^{1}H NMR signal at δ 4.45 ppm (3-OH), δ 4.50 ppm (1-OH) and δ 4.98 ppm (1-OH) being exchanged with the addition of deuterated trifluoracetic acid. Symmetrical compounds **40**–**50** had the same behaviour in ^{1}H NMR spectroscopy (see Section 3 and Table 1). The ^{13}C NMR spectra of **40**–**50** exhibited signals at δ 69–70 ppm (hydroxyl groups of 1-amino-1-deoxy-D-glucitol), at δ 156 ppm for the carbonyl group and at δ 182 ppm for the thiocarbonyl fonctionality (Table 2). The unsymmetrical ureido linkage of **50** induced two separate ^{13}C NMR signals for the carbonyl group at δ 156.0 and 156.1 ppm and four separate ^{1}H NMR signals for NH protons. The presence of two 1-amino-1-deoxy-D-glucitol or two 2-(2-aminoethoxy)ethanol moieties in unprotected compounds **40**–**50** and **61**–**71**, were confirmed from FABMS-data.

Biological evaluation.—The potential of these compounds to inhibit NAHases was studied on an enzymatic extract from *T. vaginalis* at a concentration of 100 μM. The results are reported in Table 3. Although none of the urea or thiourea derivatives showed a

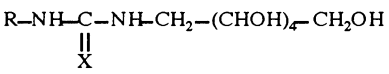


30 : X = S; R = Ph

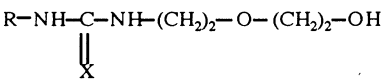
Scheme 1.



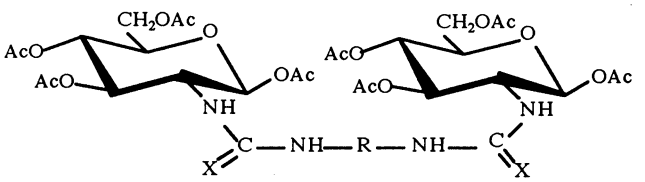
	R–	X
22	C_6H_5–	S
23	*p*-$NO_2C_6H_4$–	S
24	CH_2=$CHCH_2$–	S
25	C_6H_{11}–	O
26	1-adamantyl–	O



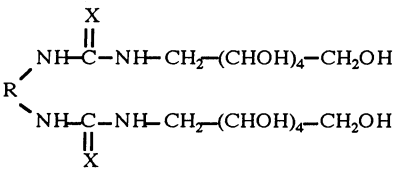
	R–	X
31	C_6H_5–	S
32	*p*-$NO_2C_6H_4$–	S
33	$C_6H_5CH_2CH_2$–	S
34	C_6H_{11}–	S
35	1-adamantyl–	S
36	CH_2=$CHCH_2$–	S
37	*p*-ClC_6H_4–	O
38	C_6H_{11}–	O
39	1-adamantyl–	O

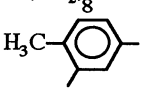


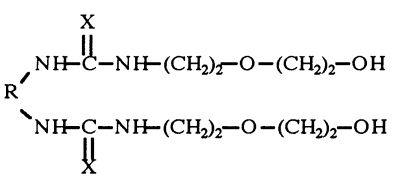
	R–	X
51	C_6H_5–	S
52	*p*-$NO_2C_6H_4$–	S
53	$C_6H_5CH_2CH_2$–	S
54	C_6H_{11}–	S
55	1-adamantyl–	S
56	CH_2=$CHCH_2$–	S
57	C_6H_5–	O
58	*p*-ClC_6H_4–	O
59	C_6H_{11}–	O
60	1-adamantyl–	O

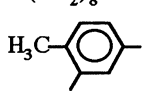


	–R–	X
27	–$(CH_2)_4$–	O
28	–$(CH_2)_6$–	O
29	–$(CH_2)_8$–	O



	–R–	X
40	–$(CH_2)_3$–	S
41	–$(CH_2)_4$–	S
42	–$(CH_2)_5$–	S
43	–$(CH_2)_6$–	S
44	–$(CH_2)_7$–	S
45	–$(CH_2)_8$–	S
46	–$(CH_2)_9$–	S
47	–$(CH_2)_4$–	O
48	–$(CH_2)_6$–	O
49	–$(CH_2)_8$–	O
50		O



	–R–	X
61	–$(CH_2)_3$–	S
62	–$(CH_2)_4$–	S
63	–$(CH_2)_5$–	S
64	–$(CH_2)_6$–	S
65	–$(CH_2)_7$–	S
66	–$(CH_2)_8$–	S
67	–$(CH_2)_9$–	S
68	–$(CH_2)_4$–	O
69	–$(CH_2)_6$–	O
70	–$(CH_2)_8$–	O
71		O

Scheme 2.

Table 1
^{1}H NMR (Me_2SO) data (δ) for compounds **40**–**50**

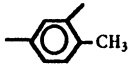
Compound	R	X	CH_2 β of NHC=S	Other aliphatic CH_2	CH, CH_2, CH_2 α of NHC=S	OH	NH
40	$(CH_2)_3$	S	1.78 (t, 2H, *J* 6.6 Hz)		3.78–3.35 (m, 20 H)	4.98 (m, 2H), 4.62 (d, 2H, *J* 5.25 Hz), 4.51 (m, 6 H)	7.73 and 7.40 (2 m, 4H)
41	$(CH_2)_4$	S	1.57 (m, 4H)		3.78–3.33 (m, 20 H)	4.97 (m, 2H), 4.61 (d, 2H, *J* 4.25 Hz), 4.52 (m, 6 H)	7.71 and 7.35 (2 m, 4H)
42	$(CH_2)_5$	S	1.58 (m, 4H)	1.39 (m, 2H)	3.78–3.32 (m, 20 H)	4.98 (m, 2H), 4.61 (d, 2H, *J* 5.06 Hz), 4.53 (m, 6 H)	7.71 and 7.35 (2 m, 4H)
43	$(CH_2)_6$	S	1.57 (m, 4H)	1.38 (m, 4H)	3.78–3.31 (m, 20 H)	4.97 (m, 2H), 4.61(d, 2H, *J* 5.33 Hz), 4.50 (m, 6 H)	7.70 and 7.35 (2t, 4H, *J* 4.85 and 4.70 Hz)
44	$(CH_2)_7$	S	1.56 (m, 4H)	1.38 (m, 6H)	3.77–3.28 (m, 20 H)	4.99 (m, 2H), 4.61 (m, 2H), 4.51 (m, 6 H)	7.71 and 7.35 (2 m, 4H)
45	$(CH_2)_8$	S	1.56 (m, 4H)	1.38 (m, 8H)	3.78–3.31 (m, 20 H)	4.98 (m, 2H), 4.61 (m, 2H), 4.51 (m, 6 H)	7.70 and 7.34 (2 m,4H)
46	$(CH_2)_9$	S	1.55 (m, 4H)	1.37 (m, 10H)	3.77–3.48 (m, 20 H)	4.98 (m, 2H), 4.61 (m, 2H), 4.54 (m, 6 H)	7.71 and 7.35 (2 m, 4H)
	R	X	CH_2 β of NHC=O	Other CH, CH_2	CH, CH_2,CH_2 α of NHC=O	OH	NH
47	$(CH_2)_4$	O	1.44 (m, 4H)		3.68–3.06 (m, 20H)	4.92 and 4.58 (2d, 4H, *J* 5.3 and 3.9 Hz), 4.45 (m, 6H)	6.16 and 5.92 (2t, 4H, *J* 5.4 and 5.5 Hz)
48	$(CH_2)_6$	O	1.44 (m, 4H)	1.35 (m, 4H)	3.64–3.06 (m, 20H)	4.92 and 4.58 (2m, 4H), 4.45 (m, 6H)	6.13 and 5.90 (2t, 4H, *J* 5.2 and 4.9 Hz)
49	$(CH_2)_8$	O	1.44 (m, 4H)	1.35 (m, 8H)	3.64–3.07 (m, 20H)	4.92 and 4.58 (2d, 4H, *J* 5.3 and 3.9 Hz), 4.40 (m, 6H)	6.13 and 5.90 (2t, 4H, *J* 5.3 and 5.1 Hz)
50		O		2.20 (s, 3H, CH_3), 7.03(d, 1H, *J* 8.4 Hz, ar), 7.23(dd, 1H, *J* 1.9 Hz, ar), 7.83 (m, 1H, ar)	3.71–3.08 (m, 16H)	4.95 (m, 2H), 4.60 (m, 2H), 4.46 (m, 6H)	6.73 and 6.17 (2t, 2 H, *J* 4.7 Hz), 8.61 (s, 1H), 7.82 (m, 1H)

Table 2
^{13}C NMR (Me_2SO) data (δ) for compounds **40**–**50**

Compound	X	Aminodeoxyglucitol				Alkyl			Aryl
		CH_2NH	CH(OH)	CH_2OH	C=X	$CH_2\alpha NH$	$CH_2\beta NH$	Others	
40	S	46.9	71.9, 71.5, 70.0	63.4	182.3	41.5	28.8		
41	S	46.9	71.9, 71.5, 70.0	63.4	182.3	43.5	26.4		
42	S	46.8	71.9, 71.4, 70.0	63.4	182.3	43.6	28.5	23.9	
43	S	46.8	71.9, 71.4, 70.0	63.4	182.2	43.8	28.7	26.2	
44	S	47.9	72.7, 72.0, 71.6, 71.5 71.2, 70.7, 70.3, 70.0	63.7	182.4	43.7	28.9	28.9 and 26.6	
45	S	46.8	71.9, 71.4, 70.0	63.3	182.2	43.8	28.8	28.8 and 26.4	
46	S	47.0	72.1, 71.7,71.6, 71.1 70.7, 70.5, 70.1	63.5	182.4	43.9	29.0	29.0 and 26.6	
47	O	42.5	72.6, 72.1, 71.5, 69.6	63.4	158.6	39.3	27.5		
48	O	42.5	72.6, 72.1, 71.5, 69.6	63.4	158.7	39.3	30.0	26.2	
49	O	42.4	72.5, 72.0, 71.5, 69.6	63.3	158.6	39.3	29.9		
50	O	42.5	72.4, 72.1, 71.8, 70.2	63.7	156.0 156.1				138.8 and 138.5 (C–NH) 130.4, 120.0, 112.2, 110.8 17.6 (CH_3)

Table 3
Inhibition level of NAHases with an inhibitor concentration of 100 μM

Compound	Inhibition (%)	Compound	Inhibition (%)	Compound	Inhibition (%)
22	26	**40**	17	**58**	26
23	17	**41**	0	**59**	27
24	36	**42**	10	**60**	41
25	19	**43**	3	**61**	22
26	29	**44**	4	**62**	10
27	31	**45**	13	**63**	27
28	46	**46**	30	**64**	22
29	30	**47**	24	**65**	11
30	0	**48**	46	**66**	24
31	11	**49**	25	**67**	8
32	16	**50**	38	**68**	32
33	24	**51**	32	**69**	22
34	2	**52**	16	**70**	27
35	54	**53**	34	**71**	31
36	25	**54**	48	**TAG**[a]	31
37	5	**55**	24	**AEE**[b]	28
38	28	**56**	19	**ADG**[c]	27
39	25	**57**	ND	**GlcN**[d]	25

[a] 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose.
[b] 2-(2-Aminoethoxy)ethanol.
[c] 1-Amino-1-deoxy-D-glucitol.
[d] 2-Amino-2-deoxy-β-D-glucopyranose.

complete inhibition at 100 μM, compounds **24**, **28**, **35**, **48** and **54** showed a significant inhibition of *T. vaginalis* NAHase. The tetra-*O*-acetyl-2-deoxy-β-D-glucose thiourea or urea derivatives **24** and **28** were better inhibitors than tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose itself (31%). 1-Amino-1-deoxy-D-glucitol showed a moderate inhibition (27%) as tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose, but the related thiourea or urea analogues **35** and **48** exhibited a more potent efficiency with respective inhibition levels for NAHase of 54% for **35** and 46% for **48**. The same inhibition levels were also obtained with the 2-(2-aminoethoxy)ethanol derivatives **54** (48%) and **60** (41%).

Glycosylureas related to trehazolin were reported recently [9] with CI_{50} between 270 to 400 μM against β-glucosidases. These compounds, where the urea moiety is engaged in an oxazoline ring, are less potent inhibitors than urea **28** and **48** or thiourea **35** and **54** derivatives (inhibition around 50% of NAHase at a concentration of 100 μM). The efficiency of compounds **22**–**29**, **31**–**33**, **35**, **36**, **38**–**40**, **42**, **45**, **56**, **58**–**71** for NAHase inhibition is also better than deoxynojirimicin analogues which showed no complete (0–91%) inhibition at a concentration of 1 mM [4e].

These results, and a preliminary kinetic study showing that **48** is a competitive inhibitor of the enzyme (K_i 30 μM), are of interest for the further design of inhibitors against *T. vaginalis* NAHase which could be helpful in order to elucidate the role of the enzyme in the parasite.

3. Experimental

Materials and methods.—Phenyl isothiocyanate (**1**), *p*-nitrophenyl isothiocyanate (**2**), allyl isothiocyanate (**3**), phenethyl isothiocyanate (**4**), cyclohexyl isothiocyanate (**5**), 1-adamantyl isothiocyanate (**6**), 1-adamantyl isocyanate (**7**), cyclohexyl isocyanate (**8**), *p*-chlorophenyl isocyanate (**9**), phenyl isocyanate (**10**), 4-methyl-1,3-phenylene diisocyanate (**11**), 1,4-diisocyanatobutane (**12**), 1,6-diisocyanatohexane (**13**), 1,8-diisocyanatooctane (**14**), diamines, 1-amino-1-deoxy-D-glucitol, 2-amino-2-deoxy-β-D-glucose·HCl, 2-aminoethoxyethanol were purchased from Aldrich and used without further purification.

Melting points were determined on a Kofler apparatus. IR spectra (KBr discs or liquid films) were recorded on a Perkin–Elmer model 983 G. ^1H and ^{13}C NMR spectra were collected on a Bruker 200 spectrometer. FAB mass spectra were recorded with a NERMAG R 10-10 instrument (low resolution, 8–9 keV) using a matrix consisting of 3-nitrobenzylalcohol (compounds **31**–**39** and **61**–**71**) or glycerol (compounds **40**–**50**). Optical rotations were measured on a Perkin–Elmer (model 241) micropolarimeter. TLC was performed on HF_{254} silica plates with detection by UV light or iodine. TLC were sprayed with ninhydrin to search residual amine (glucosamine, aminodeoxyglucitol or aminoethoxyethanol) not seen under UV light. Silica gel (70–230 mesh) was used for column chromatography.

General method for the synthesis of diisothiocyanatoalkanes **15**–**21**.—The respective diaminoalkane (200 mmol) was dissolved in NaOH (4% in water, 250 mL), and CS_2 (33.5 g, 440 mmol) was added, the mixture was stirred for 3 h at 35–40 °C. The solution was then cooled before dropping ethyl chloroformate (43.5 g, 400 mmol) and stirred up for 1 h. After extraction by $CHCl_3$, the organic layer was treated with 3 N HCl (100 mL) for 15 min at room temperature, then dried on $MgSO_4$ and $CHCl_3$ was removed under reduced pressure. The mixed diisothiocyanate–carbamate byproducts were separated by column chromatography on silica-gel (1:4 CH_2Cl_2–cyclohexane).

1,3-Diisothiocyanatopropane (**15**). A syrupy mixture from 1,3-diaminopropane (14.8 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **15** (17 g, 54%) as an amorphous product: mp 113 °C; lit. n_D^{23} 1.5750 ([6]b); IR (KBr): ν 2965 and 2930 (CH, CH_2, CH_3), 2094 (NCS), and 1443 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.76 (t, 4 H, $CH_2\alpha$NCS), 2.03 (m, 2 H, $CH_2\beta$NCS).

1,4-Diisothiocyanatobutane (**16**). A syrupy mixture from 1,4-diaminobutane (17.6 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **16** (18.6 g, 54%) as an amorphous product: mp 124 °C; lit. n_D^{23} 1.5930 [6b]; IR (KBr): ν 2939 and 2858 (CH, CH_2, CH_3), 2105 (NCS), and 1448 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.71 (t, 4H, $CH_2\alpha$NCS), 1.80 (m, 4H, $CH_2\beta$NCS).

1,5-Diisothiocyanatopentane (**17**). A syrupy mixture from 1,5-diaminopentane (20.43 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **17** (9.3 g, 25%) as an amorphous product: mp 123 °C; lit. n_D^{23} 1.5680 [6b]; IR (KBr): ν 2944 and 2863 (CH, CH_2, CH_3), 2125 (NCS), and 1448 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.57 (t, 4H, $CH_2\alpha$NCS), 1.67 (m, 4H, $CH_2\beta$NCS), 1.47 (m, 2H, others CH_2).

*1,6-Diisothiocyanatohexane (**18**).* A syrupy mixture from 1,6-diaminohexane (23.23 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **18** (13.6 g, 34%) as an amorphous product: mp 124 °C; lit. n_D^{23} 1.5630 [6b]; IR (KBr): ν 2934 and 2859 (CH, CH_2, CH_3), 2090 (NCS), and 1448 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.57 (t, 4H, $CH_2\alpha$NCS), 1.67 (m, 4H, $CH_2\beta$NCS), 1.36 (m, 4H, others CH_2).

1,7-Diisothiocyanatoheptane (**19**). A syrupy mixture from 1,7-diaminoheptane (26.04 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **19** (5.6 g, 13%) as an amorphous product: mp 122 °C; IR (KBr): ν 2952 and 2861 (CH, CH_2, CH_3), 2098 (NCS), and 1449 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 3.77 (t, 4H, $CH_2\alpha$NCS), 1.75 (m, 4H, $CH_2\beta$NCS), 1.36 (m, 6 H, others CH_2).

1,8-Diisothiocyanatooctane (**20**). A syrupy mixture from 1,8-diaminooctane (28.85 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **20** as an oil (26.4 g, 58%): n_D^{20} 1.5515; IR (film): ν 2933 and 2855 (CH, CH_2, CH_3), 2109 (NCS), and 1448 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.49 (t, 4 H, $CH_2\alpha$NCS), 1.67 (m, 4 H, $CH_2\beta$NCS), 1.37 (m, 8 H, others CH_2).

1,9-Diisothiocyanatononane (**21**). A syrupy mixture from 1,9-diaminononane (31.65 g) was chromatographed (1:4 CH_2Cl_2–cyclohexane) to yield **21** as an oil (20.3 g, 42%): n_D^{20} 1.5451; IR (film): ν 2938 and 2865 (CH, CH_2, CH_3), 2107 (NCS), and 1448 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 3.49 (t, 4H, $CH_2\alpha$NCS), 1.64 (m, 4H, $CH_2\beta$NCS), 1.37 (m, 10H, others CH_2).

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-[3-(phenyl)thioureido]-β-D-glucopyranose (**22**).—Prepared according to [8b] (1.2 g, 73%): mp 110 °C; lit. 105–107 °C [8b]; $[\alpha]_D^{25}$ +17.5° (*c* 0.4, $CHCl_3$); lit. +16° [8b]; R_f 0.77 (EtOAc). Anal. Calcd for $C_{21}H_{26}N_2O_9S$: C, 52.28; H,

5.43; N, 5.81; S, 6.64. Found: C, 52.52; H, 5.78; N, 5.60; S, 6.46.

1,3,4,6-Tetra-O-*acetyl-2-deoxy-2-[3-(*p-*nitrophenyl)thioureido]-β-*D-*glucopyranose* (**23**). —To a solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose·HCl (2 g, 5.2 mmol) in water (3 mL), $NaHCO_3$ (0.44 g, 5.2 mmol) was added. After 15 min, a solution of *p*-nitrophenylisothiocyanate **2** (0.93 g, 5.2 mmol) in dioxane (6 mL) was slowly added. The mixture was stirred up at room temperature for 4 h. After extraction with EtOAc, the organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Column chromatography purification (19:1 CH_2Cl_2–EtOAc followed by 4:1 CH_2Cl_2–EtOAc) gave **23** (1.9 g, 71%) as yellow needles: mp 91 °C (petroleum ether); $[\alpha]_D^{25}$ −44.5° (*c* 0.4, $CHCl_3$); R_f 0.81 (EtOAc); IR (KBr): λ 3337 (NH), 2941 and 2895 (CH, CH_2, CH_3), 1750 (C=O), 1596 and 1528 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 8.26 (s, 1H, RNH), 8.21 and 7.54 (2 d, 4H, *J* 9.0 Hz, ar.), 6.52 (d, 1H, *J* 9.0 Hz, C_2NH), 5.76 (d, 1H, $J_{1,2}$ 8.2 Hz, H-1), 5.18 (m, 3H, H-2, H-3, H-4), 4.23 (dd, 1H, $J_{6b\text{-}5}$ 4.6 Hz, H-6b), 4.14 (dd, 1H, $J_{6a,6b}$ 12.5 Hz, $J_{6a,5}$ 2.4 Hz, H-6a), 3.82 (m, 1H, H-5), 2.16–2.01 (4s, 12H, OAc). Anal. Calcd for $C_{21}H_{25}N_3O_{11}S$: C, 47.81; H, 4.78; N, 7.97; S, 6.07. Found: C, 48.14; H, 4.62; N, 7.61; S, 5.77.

General method for the synthesis of 2-alkylureido and thioureidoglucopyranose derivatives **24**–**26**.—To 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose·HCl [7] (2 g, 5.2 mmol) in CH_2Cl_2 (30 mL), $CaCO_3$ (0.52 g) was added in water (100 mL) and the mixture was stirred at room temperature for 30 min. The organic layer was separated, washed with water, dried ($MgSO_4$) and CH_2Cl_2 was removed under reduced pressure. The resulting amine was dissolved in CH_2Cl_2 (4 mL), and isothiocyanate **3** or isocyanate **7** or **8** (5.2 mmol) in CH_2Cl_2 (3 mL) was added, the mixture was stirred at room temperature for several hours. Compounds **24**–**26** were washed with petroleum ether and purified by column chromatography.

1,3,4,6-Tetra-O-*acetyl-2-deoxy-2-[3-(2-allyl)thioureido]-β-*D-*glucopyranose* (**24**). After column chromatography purification (1:4 EtOAc–CH_2Cl_2), an oily product (0.81 g, 35%) was formed from allyl isothiocyanate **3** (0.51 g): $[\alpha]_D^{25}$ +16.5° (*c* 0.4, $CHCl_3$); R_f 0.73 (EtOAc); IR (film): *v* 3362 (NH), 2955 and 2937 (CH, CH_2, CH_3), 1750 (C=O), and 1555 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 6.22 (m, 1H, NH), 6.03 (m, 1H, NH), 5.91–5.76 (m, 1H, CH_2–C*H*=CH_2), 5.69 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1), 5.20 (m, 5 H, H-2, H-3, H-4, CH_2-NH), 4.24 (dd, 1H, $J_{6b\text{-}5}$ 4.4 Hz, H-6b), 4.14 (dd, 1H, $J_{6a,6b}$ 12.5 Hz, $J_{6a,5}$ 2.2 Hz, H-6a), 4.08 (m, 2H, CH_2=CH), 3.82 (m, 1H, H-5), 2.11–2.02 (4s, 12H, OAc). Anal. Calcd for $C_{18}H_{26}N_2O_9S$: C, 48.42; H, 5.87; N, 6.28; S, 7.17. Found: C, 48.24; H, 6.25; N, 6.37; S, 6.98.

1,3,4,6-Tetra-O-*acetyl-2-deoxy-2-[3-(cyclohexyl)ureido]-β-*D-*glucopyranose* (**25**). After column chromatography purification (1:4 EtOAc–CH_2Cl_2), an amorphous product (1.4 g, 56%) was formed from cyclohexyl isocyanate **8** (0.73 g): mp 211 °C; $[\alpha]_D^{25}$ +21.5° (*c* 0.4, $CHCl_3$); R_f 0.66 (EtOAc); IR (KBr): *v* 3411 and 3338 (NH), 2938 and 2854 (CH, CH_2, CH_3), 1745 (CH_3COO,) and 1652 cm^{-1} (NH*CO*); ^1H NMR ($CDCl_3$): δ 5.68 (m, 1H, $J_{1,2}$ 8.7 Hz, H-1), 5.12 (m, 2H, H-3, H-4), 4.55 (m, 2 H, NH), 4.24 (dd, 1H, $J_{6b,5}$ 4.7 Hz, H-6b), 4.11 (dd, 1H, $J_{6a,6b}$ 12.6 Hz, $J_{6a,5}$ 1.8 Hz, H-6a), 4.03 (m, 1H, H-2), 3.82 (m, 1H, H-5), 3.46 (m, 1 H, cyclohexyl), 2.10–2.01 (4s, 12H, OAc), 1.86–1.10 (m, 10H cyclohexyl). Anal. Calcd for $C_{21}H_{32}N_2O_{10}$: C, 53.37; H, 6.83; N, 5.93. Found: C, 53.52; H, 6.98 N, 5.59.

*1,3,4,6-Tetra-*O-*acetyl-2-deoxy-2-[3-(1-adamantyl)ureido]-β-*D-*glucopyranose* (**26**). After chromatography column purification (1:4 EtOAc–CH_2Cl_2) an amorphous product (1.14 g, 42%) was formed from 1-adamantyl isocyanate **7** (0.65 g): mp 187 °C; $[\alpha]_D^{25}$ +16.5° (*c* 0.4, $CHCl_3$); R_f 0.83 (EtOAc); IR (KBr): *v* 3361, and 3291 (NH), 2910 and 2851 (CH, CH_2, CH_3), 1748 (CH_3COO), and 1652 cm^{-1} (NH*CO*); ^1H NMR ($CDCl_3$): δ 5.62 (d, 1H, $J_{1,2}$ 8.73 Hz, H-1), 5.07 (m, 2H, H-2, H-4), 4.62 (d, 1H, *J* 9.6 Hz, NH), 4.44 (s, 1H, NH), 4.22 (dd, 1H, $J_{6b\text{-}5}$ 4.65 Hz, H-6b), 4.08 (dd, 1H, $J_{6a\text{-}6b}$ 12.1 Hz, $J_{6a\text{-}5}$ 1.65 Hz, H-6a), 4.03 (m, 1H, H-2), 3.81 (m, 1H, H-5), 2.10–2.04 (4s, 12H, 4 OAc), 1.87–1.60 (m, 15H, adamantyl). Anal. Calcd for $C_{25}H_{36}N_2O_{10}$: C,

57.24; H, 6.92; N, 5.34. Found: C, 57.12; H, 6.82; N, 5.53.

General method for the synthesis of alkyl bis(ureidoglucopyranose) derivatives **27**–**29**.—To 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose·HCl [7] (2 g, 5.2 mmol) in CH_2Cl_2 (30 mL), $CaCO_3$ (0.52 g) was added in water (100 mL) and the mixture was stirred at room temperature for 30 min. The organic layer was washed with water dried ($MgSO_4$), and CH_2Cl_2 was removed under reduced pressure. The resulting amine was dissolved in CH_2Cl_2 (4 mL), and the convenient diisocyanate **12**–**14** (2.6 mmol) in CH_2Cl_2 (3 mL) was added; the mixture was stirred at room temperature for several hours. The crude residue was washed with petroleum ether and purified by column chromatography to give **27**–**29**.

1,4-Bis[3-(1,3,4,6-tetra-O-*acetyl-2-deoxy-β-D-glucopyranos-2-yl)ureido]butane* (**27**). After column chromatography purification (1:4 EtOAc–CH_2Cl_2), an amorphous product (2.2 g, 98%) was formed from 1,4-diisocyanatobutane **12** (0.36 g): mp 180 °C; $[\alpha]_D^{25}$ +30.5° (*c* 0.2, DMF); IR (KBr): *v* 3363 (NH), 2939 and 2830 (CH, CH_2, CH_3), 1750 (CH_3COO), and 1645 cm^{-1} (NH*CO*); ^1H NMR [$(CD_3)_2SO$]: δ 6.16 and 5.90 (2 m, 4H, NH), 5.87 (d, 2H, $J_{1,2}$ 8.4 Hz, H-1), 5.32 (t, 2H, *J* 9.8 Hz, H_{-3}), 4.97 (t, 2H, *J* 9.6 Hz, H_{-4}), 4.27 (dd, 2H, $J_{6a,6b}$ 12.1Hz, $J_{6a,5}$ 4.1 Hz, H-6a), 4.10 (m, 4H, H-6b and H-2), 3.94 (m, 2H, H-5), 3.05 (m, 4H, CH_2αNH), 2.14–2.02 (m, 24H, OAc), 1.39 (m, 4H, CH_2βNH). Anal. Calcd for $C_{34}H_{50}N_4O_{20}$: C, 48.92; H, 6.04; N, 6.71. Found: C, 49.07; H, 6.09; N, 7.03.

1,6-Bis[3-(1,3,4,6-tetra-O-*acetyl-2-deoxy-β-D-glucopyranos-2-yl)ureido]hexane* (**28**). After column chromatography purification (1:4 EtOAc–CH_2Cl_2), an amorphous product (1.92 g, 86%) was formed from 1,6-diisocyanatohexane **13** (0.44 g): mp 138 °C; $[\alpha]_D^{25}$ +29.5° (*c* 0.4, DMF); IR (KBr): *v* 3359 (NH), 2941 and 2829 (CH, CH_2, CH_3), 1750 (CH_3COO), and 1652 cm^{-1}(NH*CO*); ^1H NMR [$(CD_3)_2SO$]: δ 6.17 and 5.88 (2 m, 4H, NH), 5.87 (d, 2H, $J_{1,2}$ 8.3 Hz, H-1), 5.32 (t, 2H, *J* 9.8 Hz, H_{-3}), 4.96 (t, 2H, *J* 9.9 Hz, H_{-4}), 4.28 (dd, 2H, $J_{6a,6b}$ 11.6 Hz, $J_{6a,5}$ 4.4 Hz, H-6a), 4.10 (m, 4H, H-6b and H-2), 3.91 (m, 2H, H-5), 3.03 (m, 4H, CH_2αNH), 2.14–2.02 (m, 24H, OAc), 1.31 and 1.43 (m, 8H, others CH_2). Anal. Calcd for $C_{36}H_{54}N_4O_{20}$: C, 50.11; H, 6.31; N, 6.49. Found: C, 49.96; H, 6.63; N, 6.19.

1,8-Bis[3-(1,3,4,6-tetra-O-*acetyl-2-deoxy-β-D-glucopyranos-2-yl)ureido]octane* (**29**). After column chromatography purification (1:4 EtOAc–CH_2Cl_2), an amorphous product (1.2 g, 50%) was formed from 1,8-diisocyanatooctane **14** (0.51 g): mp 170 °C; $[\alpha]_D^{25}$ +29.5° (*c* 0.4, DMF); IR (KBr): *v* 3335 (NH), 2965 and 2835 (CH, CH_2, CH_3), 1744 (CH_3COO), and 1650 cm^{-1}(NH*CO*); ^1H NMR [$(CD_3)_2SO$]: δ 6.17 and 5.87 (2 m, 4H, NH), 5.85 (d, 2H, $J_{1,2}$ 8.4 Hz, H_1), 5.32 (t, 2H, *J* 9.8 Hz, H-3), 4.96 (t, 2H, *J* 9.6 Hz, H-4), 4.28 (dd, 2H, $J_{6a,6b}$ 12.4 Hz, $J_{6a,5}$ 4.7 Hz, H-6a), 4.09 (m, 4H, H-6b and H-2), 3.91 (m, 2H, H-5), 3.03 (m, 4H, CH_2αNH), 2.14–2.02 (m, 24H, OAc), 1.40 and 1.32 (m, 12H, others CH_2). Anal. Calcd for $C_{38}H_{58}N_4O_{20}$: C, 51.23; H, 6.56; N, 6.29. Found: C, 51.03; H, 6.84; N, 5.96.

General method for the synthesis of 1-alkyl and 1-aryl thioureidoglucitol derivatives **31**–**36**.—To a solution of 1-amino-1-deoxy-D-glucitol (1.8 g, 10 mmol) in water (3 mL), a solution of the corresponding isothiocyanate 1-6 (10 mmol) in dioxane (3 mL) was dropped. The mixture was stirred at room temperature for 3–4 days. The solvent was removed under reduced pressure, the resulting residue was washed with EtOAc to give a white solid recrystallised in EtOH.

*1-Deoxy-1-(3-phenylthioureido)-*D*-glucitol* (**31**). The product (0.82 g, 26%) was formed from phenyl isothiocyanate **1** (1.36 g): mp 102 °C (EtOH); $[\alpha]_D^{25}$ −12° (*c* 0.4, DMF); R_f 0.84 (EtOH); IR (KBr): *v* 3447 and 3301 (NH, OH), 1600 (C=C), and 1542 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 9.83 (s, 1H, N*H*-C_6H_5), 7.74 (m, 1H, N*H*-CH_2), 7.57 (d, 2H, *J* 7.8 Hz, ar), 7.42 (d, 2 H, *J* 8.0 Hz, ar), 7.02 (t, 1H, *J* 7.8 Hz, ar), 4.98 (m, 1H, OH), 4.66 (d, 1H, *J* 5.18 Hz, OH), 4.50 (m, 3H, OH), 3.90–3.28 (m, 8H, CH, CH_2); ^{13}C NMR [$(CD_3)_2SO$]: δ 180.5 (1C, C=S), 130.1 (1C, C-1ar), 127.6 (1C, C-4ar), 124.5 and 123.0 (4C, C-3ar, C-2ar, C-5ar, C-6ar), 71.9, 71.6, 71.2, and 70.4 (4C, CHOH), 63.5 (1C, CH_2OH), 47.3 (1C, CH_2NH). FABMS: *m*/*z*, 317 $[MH]^+$. Anal. Calcd for $C_{13}H_{20}N_2O_5S$: C, 49.35; H, 6.37; N, 8.85; S, 10.13. Found: C, 49.51; H, 6.45; N, 8.91; S, 10.41.

1 - Deoxy - 1 - (3 - p - nitrophenylthioureido)-D-*glucitol* (**32**). The product (2.85 g, 80%) was formed from *p*-nitrophenyl isothiocyanate **2** (1.80 g): mp 145 °C (EtOH); $[\alpha]_D^{25}$ + 20° (*c* 0.4, DMF); R_f 0.71 (EtOH); IR (KBr): *v* 3456 and 3327 (NH, OH), 1609 (C=C), 1534 (C=S), and 1506 cm^{-1} (NO_2); ^1H NMR [$(CD_3)_2SO$]: δ 8.43 and 8.26 (2 s, 2H, NH), 8.27 and 8.28 (2 d, 4H, *J* 9.2 Hz, ar), 5.12 (m, 1H, OH), 4.65 (m, 1H, OH), 4.57 (m, 3H, OH), 3.91–3.48 (m, 8H, CH, CH_2); ^{13}C NMR [$(CD_3)_2SO$]: δ 179.9 (1C, C=S), 146.6 (1C, C-1ar), 141.8 (1C, C-4ar), 124.7 and 120.2 (4C, C-3ar, C-2ar, C-5ar, C-6ar), 71.9, 71.6, 71.2, and 70.4 (4C, CHOH), 63.5 (1C, CH_2OH), 47.4 (1C, CH_2NH); FABMS: *m/z*, 362 $[MH]^+$. Anal. Calcd for $C_{13}H_{19}N_3O_7S$: C, 43.21; H, 5.30; N, 11.63; S, 8.87. Found: C, 42.96; H, 5.39; N, 11.63; S, 8.51.

1 - Deoxy - 1 - (3 - phenethylthioureido) - D-*glucitol* (**33**). The product (2.4 g, 69%) was formed from phenethyl isothiocyanate **4** (1.63 g): mp 123 °C (EtOH); $[\alpha]_D^{25}$ − 12° (*c* 0.4, DMF); R_f 0.88 (1:1 EtOH–EtOAc); IR (KBr): *v* 3530 and 3330 (NH, OH), 2967 and 2920 (CH, CH_2), 1645 (C=O), 1591(C=C), and 1570 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.76 (m, 1H, NH), 7.40 (m, 6H, 5 ar and 1NH), 4.98 (m, 1H, OH), 4.51 (d, 1H, *J* 5.31 Hz, OH), 4.46 (m, 3H, OH), 4.47–3.76 (m, 10H, $CH_2C_6H_5$ and CH, CH_2 glucitol), 2.90 (t, 2H, $CH_2CH_2C_6H_5$); ^{13}C NMR [$(CD_3)_2SO$]: δ 180.3 (1C, C=S), 139.5 (1C, C-1ar), 128.8 and 128.5 (4C, C-3ar, C-2ar, C-5ar, C-6ar), 126.4 (1C, C-4ar), 72.0 and 71.5, 70.0 (4C, CHOH), 63.4 (1C, CH_2OH), 45.9 (1C, CH_2NH), 43.5 and 35.0 (2C, CH_2); FABMS: *m/z*, 345 $[MH]^+$. Anal. Calcd for $C_{15}H_{24}N_2O_5S$: C, 52.30; H, 7.03; N, 8.14; S, 9.29. Found: C, 52.42; H, 6.97; N, 8.06; S, 9.65.

1 - Deoxy - 1 - (3 - cyclohexylthioureido) - D-*glucitol* (**34**). The product (1.6 g, 50%) was formed from cyclohexyl isothiocyanate **5** (1.41 g): mp 112 °C (EtOH); $[\alpha]_D^{25}$ − 6.5° (*c* 0.4, DMF); R_f 0.87 (1:1 EtOH–EtOAc); IR (KBr): *v* 3365 and 3314 (NH, OH), 2927 and 2852 (CH, CH_2), and 1555 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.62 (d, 1H, *J* 7.93 Hz, NH), 7.29 (m, 1H, NH), 4.96 (m, 1H, OH), 4.60 (d, 1H, *J* 5.35 Hz, OH), 4.45 (m, 3H, OH), 4.06 (m, 1H, NH-*CH*), 3.76–3.30 (m, 8H, CH, CH_2 glucitol), 1.97–1.22 (m, 10H, cyclohexyl); ^{13}C NMR [$(CD_3)_2SO$]: δ 181.2 (1C, C=S), 71.8, 71.5, 71.4 and 70.1 (4C, CHOH), 63.4 (1C, CH_2OH), 51.8 (1C, CHNH), 46.7 (1C, CH_2NH), 32.4, 25.3 and 24.5 (5C, CH_2); FABMS: *m/z*, 323 $[MH]^+$. Anal. Calcd for $C_{13}H_{26}N_2O_5S$: C, 48.42; H, 8.13; N, 8.69; S, 9.92. Found: C, 48.37; H, 8.47; N, 8.85; S, 9.56.

1 - Deoxy - 1 - (3 - adamantylthioureido) - D-*glucitol* (**35**). The product (1.8 g, 51%) was formed from 1-adamantylisothiocyanate **6** (1.93 g): mp 137 °C (EtOH); $[\alpha]_D^{25}$ not determined due to poor solubility in appropriate solvent; R_f 0.85 (1:1 EtOH–EtOAc); IR (KBr): *v* 3337 and 3301 (NH, OH), 2907 and 2859 (CH, CH_2), and 1559 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.37 (m, 2H, NH), 4.98 (m, 1H, OH), 4.63 (m, 1H, OH), 4.51 (m, 3H, OH), 3.70–3.10 (m, 8H, CH, CH_2 glucitol), 2.25–1.70 (m, 15H, adamantyl); FABMS: *m/z*, 375 $[MH]^+$. Anal. Calcd for $C_{17}H_{30}N_2O_5S$: C, 54.52; H, 8.07; N, 7.48; S, 8.56. Found: C, 54.85; H, 8.00; N, 7.39; S, 8.26.

1-Deoxy-1-(3-allylthioureido)-D-*glucitol* (**36**). The product (1.3 g, 53%) was formed from allylisothiocyanate **3** (1.0 g): mp 113 °C (EtOH); $[\alpha]_D^{25}$ − 9° (*c* 0.4, DMF); R_f 0.87 (1:1 EtOH–EtOAc); IR (KBr): *v* 3293 (NH, OH), 2954 and 2877 (CH, CH_2), and 1559 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.82 and 7.47 (2 m, 2H, NH), 6.00–5.87 (m, 1H, CH=CH_2), 5.23 (m, 2H, CH_2–CH=CH), 4.99 (m, 1H, OH), 4.61 (d, 1H, *J* 5.34 Hz, OH), 4.45 (m, 3H, OH), 4.16 (m, 2H, CH=CH_2), 3.80–3.50 (m, 8H, CH, CH_2 glucitol); ^{13}C NMR [$(CD_3)_2SO$]: δ 182.2 (1C, C=S), 135.2 and 115.5 (2C, CH=CH_2), 71.9, 71.4, and 70.0 (4C, CHOH), 63.4 (1C, CH_2OH), 46.9 and 46.1 (2C, CH_2NH); FABMS: *m/z*, 281 $[MH]^+$. Anal. Calcd for $C_{10}H_{20}N_2O_5S$: C, 42.84; H, 7.19; N, 9.99; S, 11.44. Found: C, 42.44; H, 7.38; N, 10.26; S, 11.20.

General method for the synthesis of 1-alkyl and 1-aryl ureido-D-*glucitol derivatives* **37**–**39**.—A solution of the respective isocyanate **7**–**9** (20 mmol) in dioxane (5 mL) was added to 1-amino-1-deoxy-D-glucitol (3.7 g, 20 mmol) in water (4 mL) and stirred at room temperature. After 4–10 h, the solid residue was separated by filtration, washed (EtOAc) resulting in a white powder.

1-Deoxy-1-(3-p-chlorophenylureido)-D-glucitol (**37**). The product (2.8 g, 42%) was formed from *p*-chlorophenylisocyanate **9** (3.07g): mp 180 °C (EtOH); $[\alpha]_D^{25}$ −9.5° (*c* 0.4, DMF); R_f 0.82 (1:1 EtOH–EtOAc); IR (KBr): *v* 3529 (NH), 3330 (OH), 2967 and 2920 (CH, CH_2), 1645 (C=O), 1591 and 1570 cm^{-1} (C=C); ^1H NMR [$(CD_3)_2SO$]: δ 8.89 (s, 1H, NH), 7.53 and 7.36 (2 d, 4 H, ar), 6.27 (t, 1H, *J* 4.54 Hz, *NH*–CH_2), 4.96 (d, 1H, *J* 4.10 Hz, OH), 4.59 (d, 1H, *J* 5.33 Hz, OH), 4.47 (m, 3H, OH), 3.71–3.14 (m, 8H, CH, CH_2 glucitol); ^{13}C NMR [$(CD_3)_2SO$)]: δ 155.3 (1C, CO), 139.7 (1C, C-1ar), 128.6 (1C, C-4ar), 124.4, and 119.1 (4C, C-2ar, C-3ar, C-5ar, C-6ar), 72.0, 71.7, 71.5 and 70.1 (4C, CHOH), 63.5 (1C, CH_2OH), 42.2 (1C, CH_2NH); FABMS: *m*/*z*, 335 $[MH]^+$. Anal. Calcd for $C_{13}H_{19}ClN_2O_6$: C, 46.64; H, 5.72; N, 8.37. Found: C, 46.69; H, 5.93; N, 8.54.

1-Deoxy-1-(3-cyclohexylureido)-D-glucitol (**38**). The product (0.73 g, 12%) was formed from cyclohexylisocyanate **8** (2.82 g): mp 180 °C (EtOH); $[\alpha]_D^{25}$ +6°(*c* 0.2, DMF); R_f 0.77 (1:1 EtOH–EtOAc); IR (KBr): *v* 3415 and 3371 (NH, OH), 2927 and 2852 (CH, CH_2), and 1626 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 6.08 (d, 1H, *J* 7.9 Hz, NH), 5.85 (t, 1H, *J* 5.4 Hz, NH), 4.93 (d, 1H, *J* 3.95 Hz, OH), 4.58 (d, 1H, *J* 5.13 Hz, OH), 4.45 (m, 3H, OH), 3.76–3.38 (m, 8H, CH, CH_2 glucitol), 3.05 (m, 1H, H_1 cyclohexyl), 1.86–1.12 (m, 10H cyclohexyl); ^{13}C NMR [$(CD_3)_2SO$]: δ 157.8 (1C, C=O), 72.4 71.2, 71.5 and 69.6 (4C, CHOH), 63.5 (1C, CH_2OH), 47.6 (1C, CHNH), 42.3 (1C, CH_2NH), 32.4, 25.8 and 24.5 (5C, CH_2); FABMS: *m*/*z*, 307 $[MH]^+$). Anal. Calcd for $C_{13}H_{26}N_2O_6$: C, 50.97; H, 8.55; N, 9.14. Found: C, 51.11; H, 8.62; N, 8.89.

1-Deoxy-1-[3-(1-adamantyl)ureido]-D-glucitol (**39**). The product (2.1 g, 30%) was formed from 1-adamantylisocyanate **7** (1.77 g): mp 178 °C (EtOH); $[\alpha]_D^{25}$ +2.7° (*c* 0.2, DMF); R_f 0.66 (1:1 EtOH–EtOAc); IR (KBr): *v* 3340 and 3200 (NH, OH), 2909 and 2865 (CH, CH_2), and 1620 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 5.89 (s, 1H, NH), 5.82 (t, 1H, *J* 5.11 Hz, NH), 4.87 (d, 1H, *J* 4.17 Hz, OH), 4.57 (d, 1H, *J* 5.99 Hz, OH), 4.44 (m, 3H, OH), 3.70–2.96 (m, 8H, CH, CH_2 glucitol), 2.09–1.71 (m, 15H, adamantyl); FABMS: *m*/*z*, 307 $[MH]^+$). Anal. Calcd for $C_{17}H_{30}N_2O_6$: C, 56.97; H, 8.44; N, 7.82. Found: C, 57.01; H, 8.47; N, 7.75.

General method for the synthesis of bis(thioureido)derivatives **40**–**46**.—To a solution of 1-amino-1-deoxy-D-glucitol (3.7 g, 20 mmol) in water (3 mL), the corresponding diisothiocyanatoalkane **15**–**21** (10 mmol) in dioxane (3 mL) was slowly added. The mixture was stirred at room temperature for 3–4 days. The solvent was removed under reduced pressure, the resulting residue was washed (EtOAc) resulting in a white solid compound.

1,3-Bis{1-[3-(1-deoxy-D-glucit-1-yl)]thioureido}propane (**40**). The product (4.1 g, 80%) was formed from 1,3-diisothiocyanatopropane **15** (1.60 g): mp 114 °C (EtOH); $[\alpha]_D^{25}$ −9° (*c* 0.4, DMF); R_f 0.43 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3507–3276 (NH, OH), 2960 and 2825 (CH, CH_2), and 1570 cm^{-1} (C=S); FABMS: *m*/*z*, 521 $[MH]^+$. Anal. Calcd for $C_{17}H_{36}N_4O_{10}S_2$: C, 39.22; H, 6.97; N, 10.76; S, 12.32. Found: C, 39.44; H, 7.17; N, 10.38; S, 12.63.

1,4-Bis{1-[3-(1-deoxy-D-glucit-1-yl])thioureido}butane (**41**). The product (4.9 g, 93%) was formed from 1,4-diisothiocyanatobutane **16** (1.72 g): mp 119 °C (EtOH); $[\alpha]_D^{25}$ −6.5 °C (*c* 0.4, DMF); R_f 0.50 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3450 and 3154 (NH, OH), 2970 and 2865 (CH, CH_2), and 1560 cm^{-1} (C=S); FABMS: *m*/*z*, 535 $[MH]^+$. Anal. Calcd for $C_{18}H_{38}N_4O_{10}S_2$: C, 40.44; H, 7.16; N, 10.48; S, 11.99. Found: C, 40.30; H, 7.33; N, 10.24; S, 12.22.

1,5-Bis{1-[3-(1-deoxy-D-glucit-1-yl)]thioureido}pentane (**42**). The product (3.8 g, 70%) was formed from 1,5-diisothiocyanatopentane **17** (1.86 g): mp 133 °C (EtOH); $[\alpha]_D^{25}$ −6.7° (*c* 0.4, DMF); R_f 0.57 (2:2:1 MeOH–EtOAc–aq ammonia; IR (KBr): *v* 3375 and 3205 (NH, OH), 2956 and 2882 (CH, CH_2), and 1560 cm^{-1} (C=S); FABMS: *m*/*z*, 549 $[MH]^+$. Anal. Calcd for $C_{19}H_{40}N_4O_{10}S_2$: C, 41.59; H, 7.35; N, 10.21; S, 11.69. Found: C, 41.74; H, 7.58; N, 10.32; S, 11.84.

1,6-Bis{1-[3-(1-deoxy-D-glucit-1-yl)]thioureido}hexane (**43**). The product (1.12 g, 20%) was formed from 1,6-diisothiocyanatohexane **18** (2.0 g): mp 126 °C (EtOH); $[\alpha]_D^{25}$ −7° (*c* 0.4,

DMF); R_f 0.63 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3450 and 3198 (NH, OH), 2928 and 2897 (CH, CH_2), and 1559 cm^{-1} (C=S); FABMS: *m/z*, 563 $[MH]^+$. Anal. Calcd for $C_{20}H_{42}N_4O_{10}S_2$: C, 42.69; H, 7.52; N, 9.96; S, 11.40. Found: C, 42.80; H, 7.45; N, 10.06; S, 11.29.

*1,7-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]thioureido}heptane* (**44**). The product (3.2 g, 56%) from 1,7-diisothiocyanatoheptane **19** (2.14 g): mp 130 °C (EtOH); $[\alpha]_D^{25}$ −6.7° (*c* 0.4, DMF); R_f 0.68 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3450 and 3197 (NH, OH), 2910 and 2859 (CH, CH_2), and 1555 cm^{-1} (C=S); FABMS: *m/z*, 577 $[MH]^+$. Anal. Calcd for $C_{21}H_{44}N_4O_{10}S_2$: C, 43.74; H, 7.69; N, 9.71; S, 11.12. Found: C, 43.65; H, 7.93; N, 9.86; S, 10.73.

*1,8-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]thioureido}octane* (**45**). The product (4.2 g, 71%) was formed from 1,8-diisothiocyanatooctane **20** (2.30 g): mp 138 °C (EtOH); $[\alpha]_D^{25}$ −6.5° (*c* 0.4, DMF); R_f 0.73 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3500 and 3202 (NH, OH), 2910 and 2859 (CH, CH_2), and 1562 cm^{-1} (C=S); FABMS: *m/z*, 591[MH]$^+$. Anal. Calcd for $C_{22}H_{46}N_4O_{10}S_2$: C, 44.73; H, 7.85; N, 9.48; S, 10.85. Found: C, 44.47; H, 7.93; N, 9.86; S, 11.07.

*1,9-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]thioureido}nonane* (**46**). The product (3.3 g, 55%) was formed from 1,9-diisothiocyanatononane **21** (2.42 g): mp 128 °C (EtOH); $[\alpha]_D^{25}$ −6.5° (*c* 0.4, DMF); R_f 0.76 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3378 and 3199 (NH, OH), 2930 and 2869 (CH, CH_2), and 1565 cm^{-1} (C=S). Anal. Calcd for $C_{23}H_{48}N_4O_{10}S_2$: C, 45.68; H, 8.00; N, 9.26; S, 10.85. Found: C, 45.83; H, 8.28; N, 8.90; S, 10.92.

General method for synthesis of bis(glucityl-ureido)compounds **47**–**50**.—A solution of the convenient diisocyanate **11**–**14** (10 mmol) in dioxane (5 mL) was added to 1-amino-1-deoxy-D-glucitol (3.7g, 20 mmol) in water (4 mL) and stirred at room temperature for 4–10 h. A solid residue was then isolated by filtration, washed by EtOAc and hot EtOH.

*1,4-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]ureido}butane* (**47**). An amorphous product (1.8 g, 36%) was formed from 1,4-diisocyanatobutane **12** (1.40 g): mp 154 °C; $[\alpha]_D^{25}$ was not determined due to low solubility in all convenient solvents; IR (KBr): *v* 3500 and 3205 (NH, OH), 2941, 2879 and 2863 (CH, CH_2), and 1616 cm^{-1} (C=O); FABMS: *m/z*, 503 $[MH]^+$. Anal. Calcd for $C_{18}H_{38}N_4O_{12}$: C, 43.01; H, 7.63; N, 11.15. Found: C, 42.66; H, 7.52; N, 11.04.

*1,6-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]ureido}hexane* (**48**). An amorphous product (4.8 g, 93%) was formed from 1,6-diisocyanatohexane **13** (1.68 g): mp 170 °C; $[\alpha]_D^{25}$ was not determined due to low solubility in all convenient solvents; IR (KBr): *v* 3500 and 3199 (NH, OH), 2920 and 2840 (CH, CH_2), and 1516 cm^{-1} (C=O); FABMS: *m/z*, 531 $[MH]^+$. Anal. Calcd for $C_{20}H_{42}N_4O_{12}$: C, 45.26; H, 7.98; N, 10.56. Found: C, 45.30; H, 7.60; N, 10.75%.

*1,8-Bis{1-[3-(1-deoxy-*D*-glucit-1-yl)]ureido}octane* (**49**). An amorphous product (1.9 g, 34%) was formed from 1,8-diisocyanatooctane **14** (1.96 g): mp 146 °C; $[\alpha]_D^{25}$ was not determined due to low solubility in all convenient solvents; IR (KBr): *v* 3500 and 3250 (NH, OH), 2930 and 2835 (CH, CH_2), and 1620 cm^{-1} (C=O); FABMS *m/z*, 559 $[MH]^+$. Anal. Calcd for $C_{22}H_{46}N_4O_{12}$: C, 47.30; H, 8.30; N, 10.03. Found: C, 47.52; H, 7.60; N, 10.56.

*1,3-Bis[3-(1-deoxy-*D*-glucit-1-yl)ureido]-4-methylbenzene* (**50**). An amorphous product (4.3 g, 80%) was formed from 4-methyl-1,3-phenylenediisocyanate **11** (1.74 g): mp 142 °C; $[\alpha]_D^{25}$ +8° (*c* 0.4, DMF); R_f 0.41 (2:2:1 MeOH–EtOAc–aq ammonia); IR (KBr): *v* 3500 and 3195 (NH, OH), 2935 and 2830 (CH, CH_2) and 1635 cm^{-1} (C=O); FABMS: *m/z*, 537 $[MH]^+$. Anal. Calcd for $C_{21}H_{36}N_4O_{12}$: C, 46.99; H, 6.77; N, 10.45. Found: C, 47.14; H, 6.51; N, 10.81.

[2-(3-Phenylthioureido)-2-ethoxy]ethanol (**51**).—A solution of phenylisothiocyanate **1** (2.1 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in the same solvent (2 mL). The mixture was stirred at room temperature for 8 h. The solvent was removed and the residue washed in hot petroleum ether to give **51** (4.2 g, 93%): mp 94 °C (EtOH); R_f 0.42 (EtOAc); IR (KBr): *v* 3276 (NH, OH), 2916, 2902 and 2875 (CH, CH_2), 1610 (C=C), and 1565 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 9.74 and 7.84

(2 s, 2H, NH), 7.70 (t, 2H, *J* 7.7 Hz, ar), 7.56 (d, 2H, *J* 7.6 Hz, ar), 7.21 (t, 1H, *J* 7.2 Hz, ar), 4.77 (t, 1H, *J* 5.1 Hz, OH), 3.80–3.56 (m, 8H, CH_2). Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.72; N, 11.66; S, 13.32. Found: C, 55.06; H, 6.40; N, 12.05; S, 13.69.

[2-(3-p-Nitrophenylthioureido)-2-ethoxy]-ethanol (**52**).—A solution of *p*-nitrophenyl isothiocyanate **2** (2.9 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol)) in dioxane (2 mL). The solution was stirred at room temperature for 3 h. The solvent was removed and the residue washed with hot petroleum ether to give **52** (4.8 g, 89%): mp 147 °C (EtOH); R_f 0.53 (EtOAc); IR (KBr): *v* 3400 and 3247 (NH, OH), 2927 and 2914 (CH, CH_2), 1595 (C=C), and 1527 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 10.43 (s, 1H, NH-ar), 8.49 (m, 1H, NH), 8.32 and 7.96 (2d, 4H, *J* 9.2Hz, ar), 4.79 (m, 1H, OH), 3.77–3.48 (m, 8H, CH_2). Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.30; H, 5.30; N, 14.74; S, 11.22. Found: C, 46.44; H, 5.58; N, 14.39; S, 11.05.

[2-(3-Phenethylthioureido)-2-ethoxy]ethanol (**53**).—A solution of phenethyl isothiocyanate **4** (3.1 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (1:1 CH_2Cl_2–EtOAc) to give the oily compound **53** (3.9 g, 78%); R_f 0.50 (EtOAc); IR (film): *v* 3303 (NH, OH), 2929 and 2871 (CH, CH_2), and 1549 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 7.20 (m, 5 H, ar), 6.73 and 6.63 (2 m, 2 H, NH), 3.55 (m, 10 H, CH_2), 3.03 (m, 1 H, OH), 2.87 (m, 2H, CH_2-ar). Anal. Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.18; H, 7.52; N, 10.45; S, 11.92. Found: C, 58.45; H, 7.32; N, 10.09; S, 11.77.

[2-(3-Cyclohexylthioureido)-2-ethoxy]-ethanol (**54**).—A solution of cyclohexyl isothiocyanate **5** (2.7 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL). The mixture was stirred for 24 h at room temperature; after evaporation of solvent under reduced pressure, the crude residue was purified by column chromatography (1:1 CH_2Cl_2–EtOAc) to give the oily **54** (4.06 g, 87%); R_f 0.39 (EtOAc); IR (film): *v* 3400 and 3250 (NH, OH), 2928 and 2857 (CH_2), and 1544 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 6.74 (m, 1H, NH), 6.56 (d, 1H, *J* 7.7 Hz, NH), 4.05 (m, 1H, $-CH-C_5H_{10}$), 3.60 (m, 8H, CH_2), 3.23 (m, 1H, OH), 1.99–1.07 (m, 10 H, C_6H_{11}). Anal. Calcd for $C_{11}H_{22}N_2O_2S$: C, 53.63; H, 9.01; N, 11.38; S, 12.99. Found: C, 53.24; H, 8.95; N, 11.07; S, 12.84.

[2-(3-Adamantylthioureido)-2-ethoxy]-ethanol (**55**).—A solution of 1-adamantyl-isothiocyanate **6** (3.6 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in the same solvent (2 mL). The mixture was stirred for 3 h at room temperature, the solvent was removed under reduced pressure, the crude residue was washed with hot petroleum ether to give **55** (1.8 g, 32%): mp 103 °C (EtOH); R_f 0.41 (EtOAc); IR (KBr): *v* 3341 and 3291 (NH, OH), 2907 and 2863 (CH_2, CH), and 1549 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 6.34 (m, 1H, NH), 6.15 (s, 1H, NH), 3.76–3.36 (m, 8H, CH_2), 3.32 (m, 1H, OH), 2.11–1.50 (m, 15H, adamantyl). Anal. Calcd for $C_{15}H_{26}N_2O_2S$: C, 60.37; H, 8.79; N, 9.39; S, 10.72. Found: C, 60.18; H, 9.17; N, 9.57; S, 10.43.

[2-(3-Allylthioureido)-2-ethoxy]ethanol (**56**).—A solution of allyl isothiocyanate **3** (1.9 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and stirred at room temperature for 8 days. After evaporation of solvent under reduced pressure, purification of the residue by chromatography on a silica gel column (EtOAc) gave the oily compound **56** (1.7 g, 44%): R_f 0.40 (EtOAc); IR (film): *v* 3250 (NH, OH), 2925 and 2890 (CH_2), and 1554 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ 6.84 (m, 2H, NH), 5.83 (m, 1H, $CH_2-CH=CH_2$), 5.17 (m, 2H, $CH_2-CH=CH_2$), 4.07 (m, 2H, $CH_2=CH-$), 3.63 (m, 8H, CH_2), 3.19 (m, 1H, OH). Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.04; H, 7.90; N, 13.72; S, 15.67. Found: C, 47.16; H, 7.90; N, 13.60; S, 16.01.

[2-(3-Phenylureido)-2-ethoxy]ethanol (**57**).—A solution of phenyl isocyanate **10** (2.2 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and the mixture

was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the crude residue was purified on a silica gel column (1:1 CH_2Cl_2–EtOAc) to give **57** (3.7 g, 88%): mp 65 °C (EtOH); R_f 0.26 (EtOAc); IR (KBr): *v* 3344 (NH, OH), 2910 and 2891 and 2869 (CH, CH_2), and 1622 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.83 (s, 1H, NH), 7.20 (m, 4H, ar), 6.92 (m, 1H, ar), 6.15 (t, 1H, *J* 5.6 Hz, NH), 3.64–3.31 (m, 8H, CH_2), 3.05 (m, 1H, OH). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.90; H, 7.20; N, 12.50. Found: C, 58.68; H, 7.51; N, 12.32.

[2 - (3 - p - Chlorophenylureido) - 2 - ethoxy]-ethanol (**58**).—A solution of *p*-chlorophenyl isocyanate **9** (2.9 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude residue was washed with hot petroleum ether to give **58** (2.1 g, 43%): mp 109 °C (EtOH); R_f 0.19 (EtOAc); IR (KBr): *v* 3350 (NH, OH), 2927 and 2915 (CH, CH_2), and 1620 cm^{-1} (C=O); ^1H NMR [$(CD_3)_2SO$]: δ 8.83 (s, 1H, NH), 8.3 and 7.95 (2 d, 4H, *J* 8.9 Hz, ar), 6.35 (t, 1H, *J* 5.4 Hz, NH), 4.74 (t, 1H, *J* 4.9 Hz, OH), 3.94–3.56 (m, 8H, CH_2). Anal. Calcd for $C_{11}H_{15}ClN_2O_3$: C, 51.15; H, 5.86; N, 10.85. Found: C, 50.97; H, 5.89; N, 10.93.

[2 - (3 - Cyclohexylureido) - 2 - ethoxy]ethanol (**59**).—A solution of cyclohexyl isocyanate **8** (2.3 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the purification of the crude residue by column chromatography (1:19 MeOH–EtOAc) gave the oily compound **59** (3.9 g, 90%): R_f 0.17 (EtOAc); IR (film): *v* 3332 (NH, OH), 2951 and 2927 (CH, CH_2), and 1627 cm^{-1} (C=O); ^1H NMR [$(CD_3)_2SO$]: δ 5.97 (d, 1H, *J* 7.9Hz, NH), 5.88 (t, 1H, *J* 5.6 Hz, NH), 4.72 (m, 1H, OH), 3.63–3.43 (m, 7H, 3 CH_2 and $-CH-C_5H_{10}$), 3.23 (q, 2H, *J* 5.6 Hz, CH_2–NH), 1.85–1.14 (m, 10H, cyclohexyl). Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.35; H,9.63; N, 12.17. Found: C, 57.05; H, 9.25; N, 12.55.

[2 - (3 - Adamantylureido) - 2 - ethoxy]ethanol (**60**).—A solution of 1-adamantyl isocyanate **7** (4.3 g, 19 mmol) in dioxane (3 mL) was added to a solution of 2-(2-aminoethoxy)ethanol (2 g, 19 mmol) in dioxane (2 mL) and the mixture was stirred up at room temperature for 8 days. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (EtOAc) to give **60** (2.4 g, 45%): mp 125 °C (EtOH); IR (KBr): *v* 3361 (NH, OH), 2908 and 2853 (CH, CH_2), and 1628 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.92 (t, 1H, *J* 5.5 Hz, NH), 4.50 (s, 1H, NH), 3.73 (m, 2H, CH_2–OH), 3.56 (m, 4H, O–CH_2), 3.33 (dd, 2H, *J* 10.2 Hz, *J* 5.5 Hz, CH_2–NH), 2.80 (m, 1H, OH), 2.04–1.63 (m, 15H, CH adamantyl). Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.79; H, 9.29; N, 9.92. Found: C, 63.75; H, 9.46; N, 9.68.

General method for the synthesis of **61**–**71**.—A solution of the convenient diisocyanatoalkane **11**–**14** or diisothiocyanatoalkane **15**–**21** (6 mmol) in dioxane (4 mL) was added to 2-(2-aminoethoxy)ethanol (1.25 g, 12 mmol) in dioxane (4 mL) and stirred at room temperature for 3–10 days to give a solid or an oily compound. The solid residue (**62**, **64**, **66**–**71**) was isolated by filtration, washed with EtOAc and acetone. The oily compounds (**61**, **63**, **65**) were purified by column chromatography (1:4 EtOH–EtOAc).

1,3-Bis[3-(2-hydroxyethoxy)ethylthioureido]-propane (**61**). The product (2.55 g, 73%) was formed from 1,3-diisothiocyanatopropane **15** (0.94 g): n_D^{20} 1. 5769; R_f 0.32 (1:4 EtOH–EtOAc); IR (film): *v* 3400 and 3200 (NH, OH), 2965 and 2907 (CH, CH_2), and 1551 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.63 (m, 2H, NH), 7.52 (m, 2H, NH), 4.72 (t, 2H, *J* 5.3 Hz, OH), 3.65–3.50 (m, 20H, O–CH_2 and N–CH_2), 1.78 (m, 2H, βNHCS); FABMS: *m/z*, 369 $[MH]^+$. Anal. Calcd for $C_{13}H_{28}N_4O_4S_2$: C, 42.37; H, 7.67; N, 15.21; S, 17.37. Found: C, 42.26; H, 7.81; N, 15.51; S, 17.62.

1,4-Bis[3-(2-hydroxyethoxy)ethylthioureido]-butane (**62**). The product (3.44 g, 95%) was formed from 1,4-diisothiocyanatobutane **16** (1.03 g): mp 111 °C (1:9 water–MeOH); R_f 0.32 (1:4 EtOH–EtOAc); IR (KBr): *v* 3400

and 3200 (NH, OH), 2935 and 2910 (CH, CH_2), and 1551 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.62 (m, 2H, NH), 7.46 (m, 2H, NH), 4.72 (t, 2H, *J* 5.3 Hz, OH), 3.67-3.47 (m, 20H, O–CH_2 and N–CH_2), 1.57 (m, 4H, βNHCS); FABMS: *m/z*, 383 $[MH]^+$. Anal. Calcd for $C_{14}H_{30}N_4O_4S_2$: C, 43.96; H, 7.91; N, 14.66; S, 16.73. Found: C, 44.14; H, 7.80; N, 14.91; S, 16.40.

1,5-Bis[3-(2-hydroxyethoxy)ethylthioureido]-pentane (**63**). The product (1.1 g, 30%) was formed from 1,5-diisothiocyanatopentane **17** (1.12 g): n_D^{20} 1. 4774; R_f 0.35 (1:4 EtOH–EtOAc); IR (film): *v* 3300 and 3100 (NH, OH), 2965, 2929 and 2885 (CH, CH_2), and 1553 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.62 (m, 2H, NH), 7.46 (m, 2H, NH), 4.74 (t, 2H, *J* 5.2 Hz, OH), 3.65–3.47 (m, 20H, O–CH_2 and N–CH_2), 1.58 (m, 4H, βNHCS), 1.38 (m, 2H, aliphatic CH_2). Anal. Calcd for $C_{15}H_{32}N_4O_4S_2$: C, 45.43; H, 8.14; N, 14.14; S, 16.14. Found: C, 45.08; H, 8.49; N, 13.81; S, 15.89.

1,6-Bis[3-(2-hydroxyethoxy)ethylthioureido]-hexane (**64**). The product (2.3 g, 60%) was formed from 1,6-diisothiocyanatohexane **18** (1.20 g): mp 61 °C (1:9 water–MeOH);R_f 0.39 (1:4 EtOH–EtOAc); IR (KBr): *v* 3350 and 3100 (NH, OH), 2964 and 2903 (CH, CH_2), and 1551 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.58 (m, 2H, NH), 7.42 (m, 2H, NH), 4.69 (t, 2H, *J* 5.4 Hz, OH), 3.67–3.44 (m, 20H, O–CH_2 and N–CH_2), 1.55 (m, 4H, βNCS), 1.37 (m, 4H, aliphatic CH_2); FABMS: *m/z*, 411 $[MH]^+$. Anal. Calcd for $C_{16}H_{34}N_4O_4S_2$: C, 46.81; H, 8.35; N, 13.65; S, 15.59. Found: C, 46.55; H, 8.17; N, 13.97; S, 15.20.

1,7-Bis[3-(2-hydroxyethoxy)ethylthioureido]-heptane (**65**). The product (1.7 g, 42%) was formed from 1,7-diisothiocyanatoheptane **19** (1.29 g): n_D^{20} 1.5219; R_f 0.42 (1:4 EtOH–EtOAc); IR (film): *v* 3400 and 3230 (NH, OH), 2995 and 2863 (CH, CH_2), and 1558 cm^{-1} (C=S), ^1H NMR [$(CD_3)_2SO$]: δ 7.61 (m, 2H, NH), 7.43 (m, 2H, NH), 4.70 (t, 2H, *J* 5.1 Hz, OH), 3.64–3.44 (m, 20H, O–CH_2 and N–CH_2), 1.58 (m, 4H, βNCS), 1.37 (m, 6H, aliphatic CH_2); FABMS: *m/z*, 425 $[MH]^+$. Anal. Calcd for $C_{17}H_{36}N_4O_4S_2$: C, 48.09; H, 8.55; N, 13.19; S, 15.10. Found: C, 47.75; H, 8.71; N, 12.84; S, 14.83.

1,8-Bis[3-(2-hydroxyethoxy)ethylthioureido]-octane (**66**). The product (2.3 g, 55%) was formed from 1,8-diisothiocyanatooctane **20** (1.36 g): mp 67 °C (1:9 water–MeOH); R_f 0.48 (1:4 EtOH–EtOAc); IR (KBr): *v* 3300–3100 (NH, OH), 2965 and 2875 (CH, CH_2), and 1552 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.61 (m, 2H, NH), 7.44 (m, 2H, NH), 4.71 (m, 2H, OH), 3.62–3.46 (m, 20H, O–CH_2 and N–CH_2), 1.56 (m, 4H, βNCS), 1.37 (m, 8H, aliphatic CH_2). FABMS: *m/z*, 439 $[MH]^+$. Anal. Calcd for $C_{18}H_{38}N_4O_4S_2$: C, 49.29; H, 8.73; N, 12.77; S, 14.62. Found: C, 49.03; H, 9.10; N, 12.88; S, 14.40.

1,9-Bis[3-(2-hydroxyethoxy)ethylthioureido]-nonane (**67**). The product (1.8 g, 42%) was formed from 1,9-diisothiocyanatopropane **21** (1.45 g): mp 50 °C (1:9 water–MeOH); R_f 0.50 (1:4 EtOH–EtOAc); IR (KBr): *v* 3300 and 3100 (NH, OH), 2930 and 2865 (CH, CH_2), and 1555 cm^{-1} (C=S); ^1H NMR [$(CD_3)_2SO$]: δ 7.58 (m, 2H, NH), 7.43 (m, 2H, NH), 4.69 (t, 2H, *J* 5.4 Hz, OH), 3.62–3.45 (m, 20H, O–CH_2 and N–CH_2), 1.56 (m, 4H, βNHCS), 1.37 (m, 10H, aliphatic CH_2), FABMS: *m/z*, 453 $[MH]^+$. Anal. Calcd for $C_{19}H_{40}N_4O_4S_2$: C, 50.41; H, 8.91; N, 12.39; S, 14.14. Found: C, 50.13; H, 8.64; N, 12.65; S, 14.49.

1,4 - Bis[3 - (2 - hydroxyethoxy)ethylureido]-butane (**68**). The product (2.5 g, 76%) was formed from 1,4-diisocyanatobutane **12** (0.84 g): mp 137 °C (1:9 water–MeOH); R_f 0.61 (1:4 EtOH–EtOAc); IR (KBr): *v* 3300 and 3223 (NH, OH), 2941 and 2879 (CH, CH_2), and 1610 cm^{-1} (C=O); ^1H NMR [$(CD_3)_2SO$]: δ 6.05 (t, 2H, *J* 5.6 Hz, NH), 5.95 (t, 2H, *J* 5.2 Hz, NH), 4.70 (t, 2H, *J* 5.4 Hz, OH), 3.63–3.46 (m, 12H, O–CH_2), 3.23 (m, 4H, $(CH_2)_nCH_2NH$), 3.08 (m, 4H, OCH_2CH_2NH), 1.43 (s, 4H, aliphatic CH_2); FABMS: *m/z*, 351 $[MH]^+$. Anal. Calcd for $C_{14}H_{30}N_4O_6$: C, 47.97; H, 8.63; N, 15.99. Found: C, 47.70; H, 8.92; N, 15.80.

1,6 - Bis[3 - (2 - hydroxyethoxy)ethylureido]-hexane (**69**). The product (1.8 g, 50%) was formed from 1,6-diisocyanatohexane **13** (1.0 g): mp 140 °C (1:9 water–MeOH); R_f 0.67 (1:4 EtOH–EtOAc); IR (KBr): *v* 3400 and 3300 (NH, OH), 2940 and 2895 (CH, CH_2), and 1616 cm^{-1} (C=O); ^1H NMR [$(CD_3)_2SO$]: δ 6.01 (t, 2H, *J* 5.6 Hz, NH), 5.91 (t, 2H, *J* 5.5

Hz, NH), 4.69 (t, 2H, *J* 5.4 Hz, OH), 3.68–3.45 (m, 12 H, O–CH_2), 3.23 (m, 4H, $(CH_2)_nCH_2NH$), 3.05 (m, 4H, OCH_2CH_2NH), 1.45–1.34 (m, 8H, aliphatic CH_2). FABMS: *m*/*z*, 379 $[MH]^+$. Anal. Calcd for $C_{16}H_{34}N_4O_6$: C, 50.78; H, 9.05; N, 14.80. Found: C, 50.94; H, 9.25; N, 14.43.

1,8 - Bis[3 - (2 - hydroxyethoxy)ethylureido]-octane (**70**). The product (2.7 g, 70%) was formed from 1,8-diisocyanatooctane **14** (1.17 g): mp 146 °C (1:9 water–MeOH); R_f 0.64 (1:4 EtOH–EtOAc); IR (KBr): *v* 3227 (NH, OH), 2935 and 2852 (CH, CH_2), and 1610 cm^{-1} (C=O); ^1H NMR [$(CD_3)_2SO$]: δ 6.01 (m, 2H, NH), 5.92 (m, 2H, NH), 4.70 (m, 2H, OH), 3.60–3.45 (m, 12H, O–CH_2), 3.25 (m, 4H, $(CH_2)_nCH_2NH$), 3.05 (m, 4H, OCH_2CH_2NH), 1.45–1.35 (m, 12H, aliphatic CH_2); FABMS: *m*/*z*, 407 $[MH]^+$. Anal. Calcd for $C_{18}H_{38}N_4O_6$: C, 53.18; H, 9.42; N, 13.78. Found: C, 53.37; H, 9.44; N, 13.60.

1,3 - Bis[3 - (2 - hydroxyethoxy)ethylureido]-4-methylbenzene (**71**). The product (3.2 g, 88%) was formed from 4-methyl-1,3-phenylenediisocyanate **11** (1.04 g): mp 124 °C (1:9 water–MeOH); R_f 0.67 (1:4 EtOH–EtOAc); IR (KBr): *v* 3380 (NH, OH); 2927 and 2878 (CH, CH_2, CH_3), 1652 cm^{-1} (C=O), and 1595 (C=C); ^1H NMR [$(CD_3)_2SO$]: δ 8.54 (s, 1H, NH), 7.84 (s, 1H, ar), 7.76 (s, 1H, NH), 7.27 (d, 1H, *J* 8.2 Hz, ar), 7.02 (d, 1H, ar), 6.75 (t, 1H, *J* 5.3 Hz, NH), 6.18 (t, 1H, *J* 5.2 Hz, NH), 4.73 (m, 2H, OH), 3.62–3.38 (m, 12H, O–CH_2), 3.35 (m, 4H, OCH_2CH_2NH), 2.13 (s, 3H, CH_3); FABMS: *m*/*z*, 385 $[MH]^+$. Anal. Calcd for $C_{17}H_{28}N_4O_6$: C, 53.10; H, 7.34; N, 14.58. Found: C, 53.25; H, 7.04; N, 14.37.

Enzymatic tests.—The *T. vaginalis* strain (CMP: Chatenay-Malabry Parasitology), sensitive to metronidazole, was isolated in 1987 from an infected woman and stored as a stabilate in conventional medium TYM (Trypsinase–Yeast extract–Maltose) [2] containing 6% Me_2SO as cryoprotector in liquid nitrogen. Parasite culture, preparation of parasites, enzyme extraction and enzyme assays were carried out as described by Sanon et al. [2].

The enzymatic substrate, *p*-nitrophenyl 2-aceamido-2-deoxy-β-D-glucopyranoside, was purchased from Sigma Chemicals (Saint-Quentin Fallavier, France).

The potential inhibitor was dissolved in Me_2SO to obtain a 1.2 mM solution. The inhibitory assay was performed in Nunclon® 96-well plates in a final volume of 120 μL. Each well received 40 μL of 0.2 M potassium phosphate buffer pH 7, 50 μL of *T. vaginalis* protein extract, 10 μL of potential inhibitor solution at 1.2 mM to obtain a 100 μM final concentration and 20 μL of *p*-nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside solution at 35 mM (to obtain a final concentration of 6 mM). The incubation time was 24 h at 37 °C and the reaction was stopped by addition of a 50 μL 0.2 M glycine–NaOH buffer (pH 10.6). Three controls were performed: (i) 0% inhibitory effect corresponding to the presence of Me_2SO without inhibitor; (ii) 100% inhibitory effect obtained with a boiled enzyme extract; and (iii) control with inhibitor in the absence of protein extract (to assess the possible absorption of inhibitor at 405 nm). The related *p*-nitrophenol was spectrophotometrically determined at 405 nm. The results are expressed as the percentage of *T. Vaginalis* NAHases inhibition at a 100 μM inhibitor final concentration and reported in Table 3.

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