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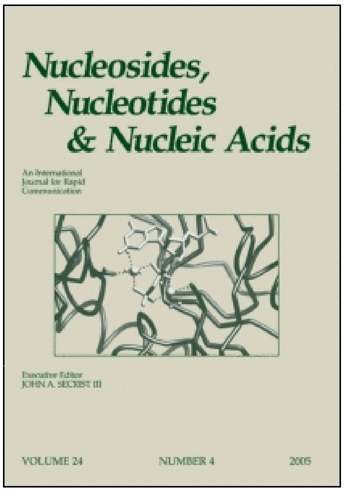

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To cite this Article Khodair, Ahmed I. and Ibrahimb, El-Said E.(1996) 'Synthesis of Hydantoin Nucleosides with Naphthylmethylene Substituents in the 5-Position', Nucleosides, Nucleotides and Nucleic Acids, 15: 11, 1927 — 1943
To link to this Article: DOI: 10.1080/07328319608002742
URL: http://dx.doi.org/10.1080/07328319608002742

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NUCLEOSIDES & NUCLEOTIDES, 15(11&12), 1927-1943 (1996)

Synthesis of Hydantoin Nucleosides with Naphthylmethylene Substituents in the 5-Position

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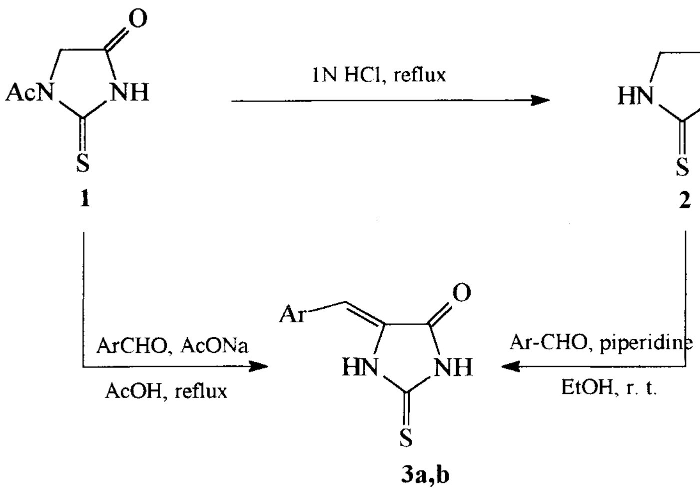
Abstract: (*Z*)-5-(Naphthylmethylene)-2-thiohydantoin derivatives (**3a,b,12a-d**) were prepared directly from condensations of 2-thiohydantoin derivatives (**1,11a,b**) with naphthaldehydes. Bisglycosylation took place on reaction of (*Z*)-5-(naphthylmethylene)-2-thiohydantoin derivatives (**3a,b**) with glycosyl halides (**4a,b**) under alkaline conditions. The bisglycosilated hydantoins produced N_3 glycosylated hydantoins on treatment with ammonia in methanol. (*Z*)-5-(2-Naphthylmethylene)-2-(benzylidene *E*-hydrazono)hydantoin (**9a**) and (*Z*)-5-(2-naphthylmethylene)-2-(polyhydroxyalkylidene *E*-hydrazono)hydantoins (**9b,c**) were prepared from the reaction of (*Z*)-5-(2-naphthyylmethylene)-2-methylmercaptohydantoin (**7**) with benzylidene *E*-hydrazone (**8a**) and monosaccharide *E*-hydrazones (**8b,c**). S-Glycosylation also took place when N_3 substituted hydantoins were reacted. The hydantoin nucleosides were tested for their potential activity against HIV and HSV.

Hydantoins substituted at C-5 are associated with a wide range of biological properties, including anticonvulsant,[1] antidepressant,[2] antiviral,[3-6] and platelet inhibitory activities,[7] and are a conspicuous structural feature of several inhibitors of aldose reductase.[8] Recently, the antiviral studies on a series of hydantoin nucleosides indicated that the most active compounds against both HSV-1 and HSV-2 were 5-(2-thienylmethylene)-3-phenyl-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin and 5-(2-thienylmethylene)-3-(4-chlorophenyl)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin.[4] In view of these observations and in continuation of our studies in the 2-glucosylation of hydantoin derivatives,[4,9] we found it interesting to investigate the synthesis and the antiviral activity of (*Z*)-5-(naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-glucoand D-galactopyranosyl)-2-thiohydantoins **5a-d**, (*Z*)-5-(naphthylmethylene)-2-(2',3',4',6'-polyhydroxyalkylmethylene *E*-hydrazono)hydantoins **9a-c** and (*Z*)-5-(naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-substituted-2-thiohydantoins **14a-h**.

Naphthaldehyde derivatives were condensed with 1-acetyl-2-thiohydantoin[10] **1** by heating in a solution of sodium acetate and acetic acid to give (*Z*)-5-(naphthylmethylene)-2-thiohydantoins **3a,b**. The same compounds could also be prepared by stirring 2-thiohydantoin[10] **2** with naphthaldehydes at room temperature in a solution of piperidine and ethanol (Scheme 1).

Compounds **3a,b** were reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and D-galactopyranosyl bromides **4a,b**[11] in the presence of aqueous potassium carbonate to give (*Z*)-5-(naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins **5a,b** and (*Z*)-5-(naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-thiohydantoins **5c,d**, respectively. The structures of compounds **5a-d** could be established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and MS). The IR spectrum of compound **5c** was characterized by the absence of signals for an NH groups at 3300 cm^{-1} and the presence of acetoxy carbonyl groups at 1760 cm^{-1}. The ^{1}H NMR spectrum of compound **5c** indicated the presence of eight OAc groups. The doublet at 5.74 ppm with spin-spin coupling constant 10.2 Hz indicated the diaxial orientation of H1' and H2' protons, indicating the presence of only the β-configuration[4]. Upon deprotection of **5a-d** with ammonia in methanol, the glucosylthio group was most likely replaced by a methoxide group in a nucleophilic substitution reaction. Subsequent demethylation afforded the N_3 glucosyl hydantoin derivatives **6a-d**. However, formation of the 2-oxo derivative directly from moisture cannot be excluded. The structures of compounds **6a-d** could be established on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and MS). The IR spectrum of compound **6a** was characterized by the absence of signals for acetoxy groups and the presence of hydroxy band at 3412 cm^{-1}. Furthermore, the signal appearing at 1767 cm^{-1} was due to C_2=O. The ^{1}H NMR (DMSO-d_6) spectrum of 5-benzylidene-3-

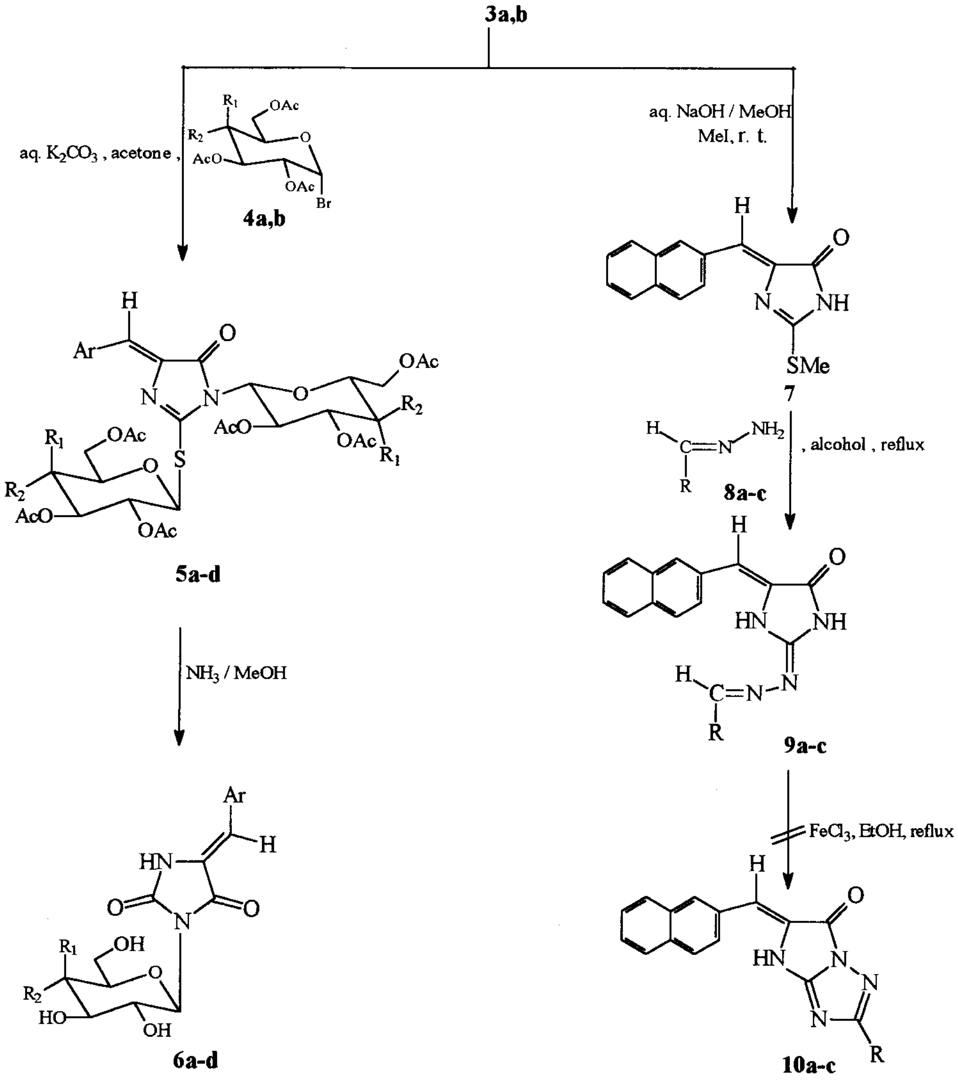


3	Ar
a	2-naphthyl
b	2-hydroxy-1-naphthyl

Scheme 1

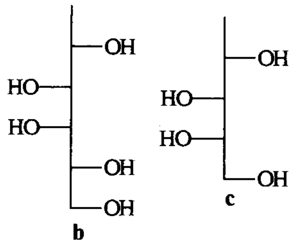
methylhydantoin has been reported to show N_1H at 10.72 ppm whereas 5-benzylidene-1-methylhydantoin showed N_3H at 11.38 ppm.[12] Thus, The ^1H NMR (DMSO-d_6) spectrum of compound **6a** revealed the presence of a singlet at 10.86 ppm due to N_1H. The multiplet at 7.42-8.47 ppm corresponded to aromatic protons. The singlet at 6.80 ppm was assigned to the vinyl proton, indicative of the *Z*-configuration of the exocyclic double bond. The doublet at 4.82 ppm due to H1' with spin-spin coupling constant 9.80 Hz which corresponds to the diaxial orientation of H1' and H2' protons, indicating the presence of the β-D-glucopyranose moiety. Compound **3a** was reacted with iodomethane in the presence of aqueous sodium hydroxide and methanol to afford the corresponding (*Z*)-5-(2-naphthylmethylene)-2-methylmercaptohydantoin **7**. When compound **7** was subjected to condensation with benzylidene *E*-hydrazone **8a**[13] or monosaccharide *E*-hydrazones **8b,c**[13] in refluxing alcohol, the corresponding (*Z*)-5-(2-naphthylmethylene)-2-(phenyl-methylene *E*-hydrazono)hydantoin **9a**, (*Z*)-5-(2-naphthylmethylene)-2-(2',3',4',5',6'-pentahydroxyhexylmethylene *E*-hydrazono)hydantoin **9b** and (Z)-5-(2-naphthylmethylene)-2-(2',3',4',5'-tetrahydroxypentylmethylene *E*-hydrazono)hydantoin **9c** were obtained, respectively. The structure of **9a-c** was established on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and MS). The ^{1}H NMR (DMSO-d_6) spectra of (*E*)- and (*Z*)-5-arylidenehydantoin derivatives have reported the vinyl proton resonance at 6.40-6.75 ppm.[5,6,12-14]. Moreover, the ^{1}H NMR (DMSO-d_6) spectrum of (*E*)-5-arylidene-2-(polyhydroxyalkylidene *E*-hydrazono)hydantoins has been reported to show the anomeric proton at δ 7.00-7.50 ppm.[13] The ^{1}H NMR (DMSO-d_6) spectrum of compound **9c** showed the presence of a singlet at δ 6.53 ppm assigned to vinyl proton. Proving *Z*-configuration of the exocyclic double bond. The doublet at δ 7.69 ppm with spin-spin coupling constant equal to 6.20 Hz corresponding to the orientation of H1' and H2' protons. Indicating the presence of the *E*-configuration of the other exocyclic double bond. El Ashry and coworkers[15-20] have reported that the alkylidene and arylidene derivatives of hydrazine linked at the α-position of heterocyclic rings could be cyclohydrogenated with a solution of iron(III) chloride in ethanol to give the corresponding 2,4-triazino heterocycles. However, attempted use of this methodology to prepare **10a-c** was unsuccessful (Scheme 2).

Naphthaldehydes were condensed with 3-substituted-2-thiohydantoins **11a,b** by stirring at room temperature in a solution of piperidine and ethanol to give (*Z*)-5-(naphthylmethylene)-3-substituted-2-thiohydantoins **12a-d** in *a quantitative* yield. When compounds **12a,b** were treated with 1.1 equivalent of aqueous NaOH in acetone followed by 1.1 equivalent of the 2,3,4,6-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl bromides **4a,b**[11], the corresponding (*Z*)-5-(2-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-substituted-2-thiohydantoins **14a-d** were obtained. For the synthesis of glucosyl hydantoins **12e-h** were likewise treated with 1.1 equivalent of aqueous K_2CO_3 in acetone followed by **4a,b**. In all cases the yields were in the range of 74-88%. The structures of compounds **14a-h** could be established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and MS). The IR spectrum of compound **14b** was characterized by the absence of signal for an NH group at 3294 cm^{-1} and the presence of acetoxy carbonyl groups at 1760 cm^{-1}. The ^{1}H NMR spectra revealed the presence of a doublet at δ 6.18 ppm with J = 10.40 Hz which corresponds



	Ar	R$_1$	R$_2$
5a	2-naphthyl	H	OAc
b	2-hydroxy-1-naphthyl	H	OAc
c	2-naphthyl	OAc	H
d	2-hydroxy-1-naphthyl	OAc	H
6a	2-naphthyl	H	OH
b	2-hydroxy-1-naphthyl	H	OH
c	2-naphthyl	OH	H
d	2-hydroxy-1-naphthyl	OH	H

R = Ph
a



Scheme 2

to the diaxial orientation of H1' and H2' protons, indicating the presence of only the β-configuration[4]. Treatment of **14b,f** with concentrated hydrochloric acid in refluxing ethanol afforded only the hydantoin derivatives **15a,b** as the unique product (a 2-thiohydantoin derivative is not formed) proving the existence of S-glycosides, this proves (*Z*)-5-(naphthylmethylene)-1-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-substituted-2-thiohydantoins **13a-h** are not formed. The structure of compounds **15a,b** could be established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR and MS). The IR spectrum of compound **15a** was characterized by the absence of signals for an acetoxy carbonyl groups and the presence of N-1H, C_2=O groups at 3290, 1717 cm^{-1}, respectively. The ^{1}H NMR spectrum of **15a** revealed the presence of a singlet at δ 6.86 ppm assigned to vinyl proton, indicating *Z*-configuration of the exocyclic double bond. The singlet at δ 12.80 ppm assigned for N_1H (Scheme 3).

The compounds **6a, c, 9c** and **14a-h** did not show any significant activity against HIV-1 (HTLV-IIIB) in MT-4 cells.[21] The same compounds were also devoid of any activity at 100 μ*M* against Herpes Simplex Virus, type 1 (HSV-1).[22]

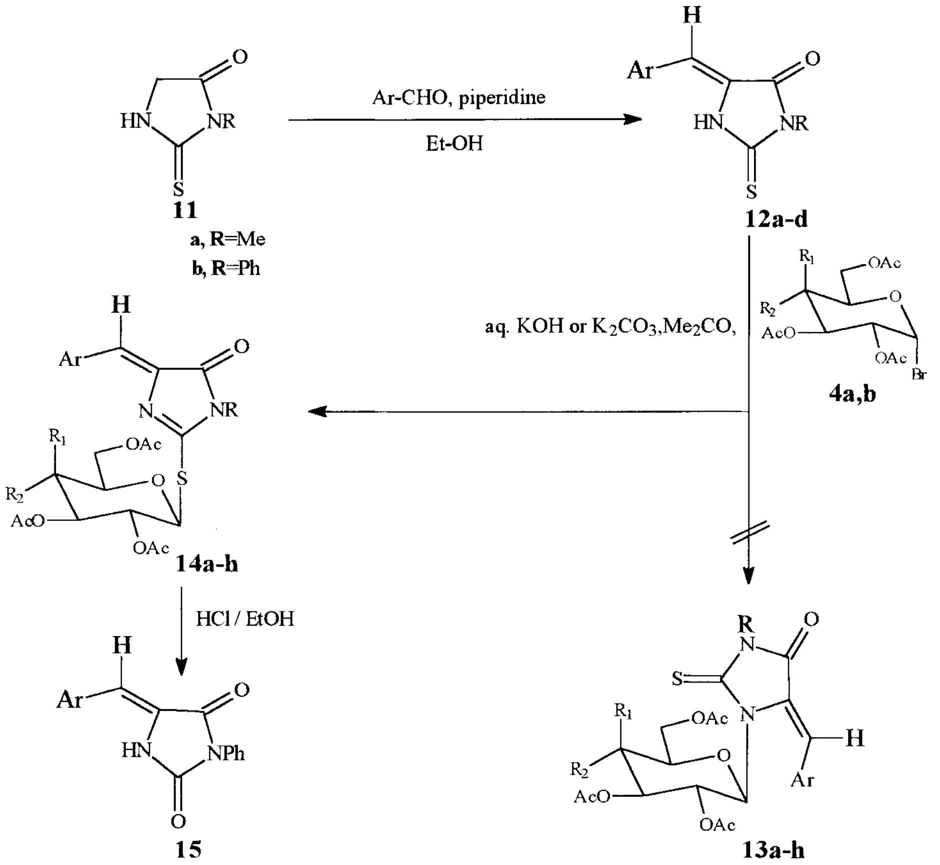
EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (KBr disc) on a Pye unicam spectra- 1000. Mass spectra were recorded on a Varian MAT 112 spectrometer. The ^{1}H-NMR spectra were recorded on a Bruker AC 250 FT spectrometer for solutions in $(CD_3)_2SO$ using TMS as internal standared. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

1-Acetyl-2-thiohydantoin (1): This compound was prepared according to the published method[10] for the preparation of 2-thiohydantoin **2**.

(*Z*)-5-(Naphthylmethylene)-2-thiohydantoins (3a,b).

Method A: A mixture of 2-naphthaldehyde (1.56 g, 10 mmol) or 2-hydroxy-1-naphthaldehyde (1.72 g, 10 mmol), anhydrous sodium acetate (2.78 g, 34 mmol) and 1-acetyl-2-thiohydantoin **1** (1.16 g, 10 mmol) in glacial acetic acid (14 ml) was heated under reflux for 2 h until the starting material was consumed (TLC with ether-benzene; 70: 30, v/v). The reaction mixture was poured into cold water. The yellow solid obtained



	Ar	R	R_1	R_2
12a	2-naphthyl	Me	-	-
b	2-naphthyl	Ph	-	-
c	2-hydroxy-1-naphthyl	Me	-	-
d	2-hydroxy-1-naphthyl	Ph	-	-
14a	2-naphthyl	Me	H	OAc
b	2-naphthyl	Ph	H	OAc
c	2-naphthyl	Me	OAc	H
d	2-naphthyl	Ph	OAc	H
e	2-hydroxy-1-naphthyl	Me	H	OAc
f	2-hydroxy-1-naphthyl	Ph	H	OAc
g	2-hydroxy-1-naphthyl	Me	OAc	H
h	2-hydroxy-1-naphthyl	Ph	OAc	H
15a	2-naphthyl	-	-	-
b	2-hydroxy-1-naphthyl	-	-	-

Scheme 3

was filtered in vacuo and recrystallized from dimethylformamide to give 2.15 g (84%) of **3a** and 2.21 g (82%) of **3b**, respectively.

Method B. To a mixture of 2-thiohydantoin **2** (10 mmol), piperidine (3 drops) and absolute ethanol (30 ml) was added 2-naphthylaldehyde (1.56 g, 10 mmol) or 2-hydroxy-1-naphthaldehyde (1.72 g, 10 mmol). The reaction mixture was stirred for 12 h at room temperature until the starting material was consumed (TLC with ether-benzene; 70: 30, v/v). The reaction mixture was diluted with cold water followed by neutralization with dilute hydrochloric acid. The resulting yellow solid was filtered in vacuo and recrystallized from dimethylformamide to give 2.32 g (91%) of **3a** and 2.51 g (93%) of **3b**, respectively.

(*Z*)-5-(2-Naphthylmethylene)-2-thiohydantoin (3a): Mp 282°C. Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02; Found: C, 65.70; H, 3.90; N, 10.80. EI MS *m/z* 254 (M^+). IR cm^{-1} (KBr) 3300 (NH), 1720 (CO), 1480 (CS). ^1H NMR (DMSO-d_6): δ 6.70 (1H, s, CH=C), 7.60-8.40 (7H, m, H_{arom}), 12.40 (1H, s, N_1H), 12.50 (1H, s, N_3H).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-thiohydantoin (3b): Mp 264°C. Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; Found: C, 62.00; H, 3.90; N, 10.20. EI MS *m/z* 270 (M^+). IR cm^{-1} (KBr) 3260 (NH), 1725 (CO), 1495 (CS). ^1H NMR (DMSO-d_6): δ 6.80 (1H, s, =CH), 7.15-7.86 (6H, m, H_{Arom}), 10.42 (1H, s, N_1H), 11.30 (1H, s, N_3H), 12.20 (1H, s, OH).

(*Z*)-5-(Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and galactopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-2-thiohydantoins (5a-d). To a solution of 2-thiohydantoins **3a,b** (5 mmol) in aqueous potassium carbonate (0.7 g, 5 mmol, in distilled water 3 ml) was added a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-gluco- or D-galactopyranosyl bromide **4** (4.52 g, 11 mmol) in acetone (30 ml). The reaction mixture was stirred for 12 h at room temperature until the starting material was consumed (TLC with ether-petroleum ether 40-60°C; 50: 50, v/v). The mixture was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the potassium bromide formed. The solid product was dried and crystallized from absolute ethanol.

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(2",3",4",6"-tetra -*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (5a): Yield 3.40 g (74%), mp 117°C. Anal. Calcd. for $C_{42}H_{46}N_2O_{19}S$: C, 55.14; H, 5.07; N, 3.06; Found: C, 55.40; H, 5.00; N, 3.30. EI MS *m/z* 914 (M^+). IR cm^{-1} (KBr) 1755 (OCO), 1720 (CO). ^{1}H NMR (DMSO-d_6): δ 1.75, 1.81, 1.92, 1.94, 1.95, 1.97, 2.02 (24H, 7s, 8Ac), 3.74-3.79 (2H, m, H5', H5"), 4.00-4.30 (4H, m, H6', H6"), 5.03-5.15 (2H, m,H4', H4"), 5.20-5.32 (4H, m, H3', H3", H2", H1"), 5.52 (1H, t, J = 9.2 Hz, H2'),5.72 (1H, d, J = 10.3 Hz, H1'), 7.03 (1H, s, CH=C), 7.40-8.40 (7H, m, H_{arom}).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoin (5b): Yield 3.36 g (72%), mp 119°C. Anal. Calcd. for $C_{42}H_{46}N_2O_{20}S$: C, 54.19; H, 4.98; N, 3.01; Found: C, 54.60; H, 5.20; N, 3.30. EI MS *m/z* 930 (M^+). IR cm^{-1} (KBr) 1757 (OCO), 1717 (NCO). ^{1}H NMR (DMSO-d_6): δ 1.79, 1.83, 1.93, 1.96, 1.98, 2.01, 2.04 (24H, 7s, 8Ac), 3.72-3.79 (2H, m, H5', H5"), 4.05-4.31 (4H, m, H6', H6"), 5.00-5.15 (2H, m,H4', H4"), 5.20-5.34(4H, m, H3', H3", H2", H1"), 5.52 (1H, t, J = 9.3 Hz, H2'),5.72 (1H, d, J = 10.1 Hz, H1'), 6.89 (1H, s, CH=C), 7.22-7.90 (6H, m, H_{Arom}).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-thiohydantoin (5c): Yield 3.60 g (76%), mp 128°C. Anal. Calcd. for $C_{42}H_{46}N_2O_{19}S$: C, 55.14; H, 5.07; N, 3.06; Found: C, 55.50; H, 4.90; N, 3.20. EI MS *m/z* 914 (M^+). IR cm^{-1} (KBr) 1760 (OCO), 1725 (NCO). ^{1}H NMR (DMSO-d_6): δ 1.76, 1.80, 1.92, 1.94, 1.95, 1.98, 2.03 (24H, 7s, 8Ac), 3.74-3.78 (2H, m, H5', H5"), 4.00-4.31 (4H, m, H6', H6"), 5.02-5.15 (2H, m, H4', H4"), 5.20-5.35 (4H, m, H3', H3", H2", H1"), 5.52 (1H, t, J = 9.0 Hz, H2'),5.74 (1H, d, J = 10.2 Hz, H1'), 7.02 (1H, s, CH=C), 7.40-8.45 (7H, m, H_{Arom}).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-(2",3",4",6"-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-thiohydantoin (5d): Yield 3.20 g (69%), mp 126°C. Anal. Calcd. for $C_{42}H_{46}N_2O_{20}S$: C, 54.19; H, 4.98; N, 3.01; Found: C, 53.90; H, 5.20; N, 3.40. EI MS *m/z* 930 (M^+). IR cm^{-1} (KBr) 1758 (OCO), 1722 (NCO).

(*Z*)-5-(Naphthylmethylene)-3-(β-D-gluco- and D-galactopyranosyl)hydantoins (6a-d): Dry gaseous ammonia was passed through a solution of the protected nucleoside **5** (2.50 mmol) in dry methanol (50 ml) at 0°C for ca. 0.5 h, and the mixture then was stirred at 0°C for 6 h until the starting material was consumed (TLC with chloroform-methanol; 90: 10, v/v). The mixture was evaporated under reduced pressure at 40°C to give a solid residue, which was crystallized from methanol.

(*Z*)-5-(2-Naphthylmethylene)-3-(β-D-glucopyranosyl)hydantoin (6a): Yield 0.73 g (73%), mp 196°C. Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00; Found: C, 60.30; H, 5.20; N, 6.70. EI MS *m/z* 400 (M^+). IR cm^{-1} (KBr) 3405 (OH, NH), 1767 (C_2=O),1725 (C_4=O). ^1H NMR (DMSO-d_6): δ 3.10 (1H, m, H4'), 3.25 (1H, m, H3'), 3.42 (2H, m, H5', H6'). 3.70 (1H, dd, J=5.5, 10.8 Hz, H6"), 4.20 (1H, m, H2'), 4.50 (1H, t, J=5.6 Hz, 6'-OH), 4.82 (1H, d, J=9.8 Hz, H1'). 5.00 (1H, d, J=5.6 Hz, 4'-OH), 5.10 (1H, d, J=5.0 Hz, 3'-OH), 5.32 (1H, d, J=4.9 Hz, 2'-OH), 6.75 (1H, s, HC=C), 7.40-8.45 (7H, m, H_{arom}), 10.56 (1H, s, N_1H).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-3-(β-D-glucopyranosyl)hydantoin (6b): Yield 0.68 g (65%), mp 183°C. Anal. Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73; Found: C, 57.90; H, 5.00; N, 7.00. EI MS *m/z* 416 (M^+). IR cm^{-1} (KBr) 3412 (OH, NH), 1770 (C_2=O),1722 (C_4=O).

(*Z*)-5-(2-Naphthylmethylene)-3-(β-D-galactopyranosyl)hydantoin (6c): Yield 0.76 g (76%), mp 212°C. Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00; Found: C, 60.30; H, 5.20; N, 7.20. EI MS *m/z* 400 (M^+). IR cm^{-1} (KBr) 3408 (OH, NH), 1755 (C_2=O),1719 (C_4=O). ^1H NMR (DMSO-d_6): δ 3.15 (1H, m, H4'), 3.25 (1H, m, H3'), 3.40 (2H, m, H5', H6'). 3.72 (1H, dd, J=5.7, 10.6 Hz, H6"), 4.20 (1H, m, H2'), 4.55 (1H, t, J=5.3 Hz, 6'-OH), 4.86 (1H, d, J=10.1 Hz, H1'). 5.05 (1H, d, J=5.7 Hz, 4'-OH), 5.20 (1H, d, J=5.1 Hz, 3'-OH), 5.35 (1H, d, J=5.0 Hz, 2'-OH), 6.80 (1H, s, HC=C), 7.47-8.45 (7H, m, H_{arom}), 10.62 (1H, s, N_1H).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-3-(β-D-galactopyranosyl)hydantoin (6d) : Yield 0.68 g (65%), mp 192°C. Anal. Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73; Found: C, 57.90; H, 4.90; N, 7.00. EI MS *m/z* 416 (M^+). IR cm^{-1} (KBr) 3410 (OH, NH), 1768 (C_2=O),1730 (C_4=O). ^1H NMR (DMSO-d_6): δ 3.12 (1H, m, H4'), 3.20 (1H, m, H3'), 3.40 (2H, m, H5', H6'). 3.70 (1H, dd, J=5.4, 10.6 Hz, H6"), 4.20 (1H, m, H2'), 4.55 (1H, t, J=5.5 Hz, 6'-OH), 4.85 (1H, d, J=10.0 Hz, H1'). 5.05 (1H, d, J=5.6 Hz, 4'-OH), 5.15 (1H, d, J=5.1 Hz, 3'-OH), 5.35 (1H, d, J=5.1 Hz, 2'-OH), 7.05 (1H, s, HC=C), 7.25-7.86 (7H, m, H_{arom}), 10.50 (1H, s, N_1H), 11.85 (1H, s, OH).

(*Z*)-5-(2-Naphthylmethylene)-2-methylmercaptohydantoin (7): 5-Naphthylmethylene-2-thiohydantoin **3a** (2.54 g, 10 mmol) was suspended in aqueous sodium hydroxide (12.60 %, 3.50 ml) at room temperature. To this suspension was added methanol (25 ml), and the mixture became clear after stirring 5 min. Methyl iodide (1.56 g, 11mmol) was added, and the mixture was stirred for 4 h at room temperature. The precipitated solid was collected by filtration and crystallized from methanol to give 2.2 g (82 %) of **7**, as yellow solid, m. p. 247°C. Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; Found: C, 66.90; H, 4.60; N, 10.20. EI MS *m/z* 268 (M^+). IR cm^{-1} (KBr) 3180 (NH), 1715 (CO); ^1H NMR (DMSO-d_6) δ 2.74 (s, 3H, SMe), 6.92 (s, 1H, CH=C), 7.54-8.61 (7H, m, H_{Arom}), 11.91 (1H, s, NH).

(*Z*)-5-(2-Naphthylmethylene)-2-(phenylmethylene *E*-hydrazono)hydantoin (9a): A mixture of **7** (1.34 g, 5 mmol) and benzylidene E-hydrazone (0.6 g, 5 mmol) in ethanol (30 ml) was heated under reflux for 24 h until the starting material was consumed (TLC with ether-petroleum ether 40-60°C; 50: 50, v/v) and the evolution of methane thiol ceased. The yellow solid, which separated, was collected and recrystallized from dimethylformamide to give 2.3 g (86%) of **9a,** as yellow solid, m. p. 285°C. Anal. Calc. for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46; Found: C, 73.90; H, 4.60; N, 16.20. EI MS *m/z* 340 (M^+). IR cm^{-1} (KBr) 3420, 3192 (NH), 1728 (CO); ^1H NMR (DMSO-d_6) δ 6.56 (s, 1H, CH=C), 7.40-8.36 (8H, m, HC=N, H_{Arom}), 10.54 (1H, br. s, N_1H), 12.88 (1H, s, N_3H).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-polyhydroxyalkylmethylene *E*-hydrazono)hydantoin (9b,c). A mixture of **7** (1.34 g, 5 mmol) and D-galactose E-hydrazone **8b** (0.97 g, 5 mmol) or L-arabinose E-hydrazone **8c** (0.82 g, 5 mmol) in methanol (30 ml) was heated under reflux for 48 h until the starting material was consumed (TLC with chloroform-methanol; 70: 30, v/v) and the evolution of methane thiol ceased. The yellow solid, which separated, was collected and recrystallized from dimethylformamide

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',5',6'-pentahydroxyhexylmethylene *E*-hydrazono)hydantoin (9b): Yield 1.3 g (63%); m. p. 237°C. Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.97; H, 5.35; N, 13.52; Found: C, 57.60; H, 5.60; N, 13.20. IR cm^{-1} (KBr) 3436 (OH), 3186 (NH), 1718 (CO). ^1H NMR (DMSO-d_6) δ 3.25-3.45 (2H, m, H6', H6''), 3.50 (2H, m, H5', H4'), 3.65 (1H, t, J = 7.6 Hz, 6'-OH), 4.20 (2H, m, 5'-OH, 4'-OH), 4.50 (3H, m, H2', H3', 3'-OH), 4.90 (1H, d, J = 7.5 Hz, 2'-OH), 7.02 (1H, s, HC=C), 7.15 (1H, d, J =5.72 Hz, H1'), 7.50-8.60 (7H, m, H_{Arom}), 10.50 (1H, br. s, N_1H), 11.65 (1H, s, N_3H).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',5'-tetrahydroxypentylmethylene *E*-hydrazono)hydantoin (9c): Yield 1.4 g (73%); m. p. 230°C. Anal. Calcd. for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58; Found: C, 59.60; H, 5.10; N, 14.30. EI MS *m/z* 384 (M^+). IR cm^{-1} (KBr) 3440 (OH), 3198 (NH), 1725 (CO). ^1H NMR (DMSO-d_6) δ 3.25-3.65 (4H, m, H5', H5'', H4'), 3.80 (1H, t, J = 6.8 Hz, 5'-OH), 4.40 (2H, m, H2', H3'), 4.60 (2H, br. s, 3'-OH, 4'-OH), 4.80 (1H, d, J = 6.6 Hz, 2'-OH), 6.53 (1H, s, HC=C), 7.51-8.34 (7H, m, H_{Arom} and H1'), 10.56 (1H, br. s, N_1H), 11.15 (1H, s, N_3H).

(*Z*)-5-Naphthylmethylene-3-substituted-2-thiohydantoins (12a-d). To a mixture of 3-substituted-2-thiohydantoin **10** (10 mmol), piperidine (3 drops) and absolute ethanol (30 ml) was added 2-naphthylaldehyde (1.56 g, 10 mmol) or 2-hydroxy-1-naphthaldehyde (1.72 g, 10 mmol). The reaction mixture was stirred 12 h at room temperature until the starting material was consumed (TLC with ether-petroleum ether 40-60°C; 50: 50, v/v). The reaction mixture was diluted with cold water followed by neutralization with diluted hydrochloric acid. The yellow solid obtained was filtered in vacuo and recrystallized from dimethylformamide to give the products **12a-d**.

(*Z*)-5-(2-Naphthylmethylene)-3-methyl-2-thiohydantoin (12a): Yield 2.3 g (86%), mp 257°C. Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; Found: C, 66.70; H, 4.60; N, 10.20. EI MS *m/z* 268 (M^+). IR cm^{-1} (KBr) 3300 (NH), 1740 (CO), 1495 (CS). ^1H NMR (DMSO-d_6): δ 3.20 (1H, s, Me), 6.76 (1H, s, CH=C), 7.60-8.40 (7H, m, H_{arom}), 12.50 (1H, s, N_1H).

(*Z*)-5-(2-Naphthylmethylene)-3-phenyl-2-thiohydantoin (12b): Yield 3.0 g (92%), mp 240°C. Anal. Calcd. for $C_{20}H_{14}N_2OS$: C, 72.70; H, 4.27; N, 8.48; Found: C, 72.50; H, 4.00; N, 8.30. EI MS *m/z* 330 (M^+). IR cm^{-1} (KBr) 3280 (NH), 1745 (CO), 1500 (CS). ^1H NMR (DMSO-d_6): δ 6.89 (1H, s, CH=C), 7.40-8.50 (12H, m, H_{arom}), 12.79 (1H, s, N_1H).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-3-methyl-2-thiohydantoin (12c): Yield 2.33 g (82%), mp 255°C. Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; Found: C, 63.00; H, 4.30; N, 9.70. EI MS *m/z* 284 (M^+). IR cm^{-1} (KBr) 3500 (OH),

3290 (NH), 1740 (CO), 1490 (CS). ^{1}H NMR (DMSO-d_6): δ 3.24 (3H, s, Me), 6.99 (1H, s, CH=C), 7.23-8.48 (6H, m, H$_{Arom}$), 11.60 (1H, s, N$_1$H), 12.10 (1H, s, OH).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-3-phenyl-2-thiohydantoin (12d): Yield 3.25 g (94%), mp 256°C. Anal. Calcd. for $C_{20}H_{14}N_2O_2S$: C, 69.35; H, 4.07; N, 8.09; Found: C, 69.00; H, 3.90; N, 7.90. EI MS *m/z* 346 (M$^+$). IR cm^{-1} (KBr) 3500 (OH), 3295 (NH), 1745 (CO), 1500 (CS).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-substituted-2-thiohydantoins (14a-d). To a solution of 2-thiohydantoins **11a,b** (5 mmol) in aqueous sodium hydroxide (6.66%, 3 ml) was added a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-gluco- or D-galactopyranosyl bromide **4** (2.26 g, 5.5 mmol) in acetone (20 ml). The reaction mixture was stirred 6 h at room temperature until the starting material was consumed (TLC with ether-petroleum ether 40-60°C; 50: 50, v/v). The mixture was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the sodium bromide formed. The solid product was dried and crystallized from absolute ethanol.

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-methyl-2-thiohydantoin (14a): Yield 2.50 g (84%), mp 186°C. Anal. Calcd. for $C_{29}H_{30}N_2O_{10}S$: C, 58.19; H, 5.05; N, 4.68; Found: C, 58.50; H, 5.30; N, 5.00. EI MS *m/z* 598 (M$^+$). IR cm^{-1} (KBr) 1756 (OCO), 1725 (NCO). ^{1}H NMR (DMSO-d_6): δ 1.65, 1.96, 2.00, 2.8 (12H, 4s, 4Ac), 3.18 (3H, s, Me), 4.05-4.24 (2H, m, H6', H6"), 4.45 (1H, dd, J=2.7, 9.8 Hz, H5'), 5.10 (1H, t, J = 9.7 Hz, H4'), 5.36 (1H, t, J = 9.8 Hz, H2'), 5.75 (1H, t, J = 9.2 Hz, H3'),6.16 (1H, d, J = 10.3 Hz, H1'), 7.25 (1H, s, CH=C), 7.40-8.76 (7H, m, H$_{arom}$).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-phenyl-2-thiohydantoin (14b): Yield 2.80 g (85%), mp 192°C. Anal. Calcd. for $C_{34}H_{32}N_2O_{10}S$: C, 61.81; H, 4.88; N, 4.24; Found: C, 62.20; H, 5.10; N, 4.00. EI MS *m/z* 660 (M$^+$). IR cm^{-1} (KBr) 1760 (OCO), 1720 (NCO). ^{1}H NMR (DMSO-d_6): δ 1.66, 1.99, 2.02, 2.09 (12H, 4s, 4Ac), 4.05-4.24 (2H, m, H6', H6"), 4.45 (1H, dd, J=2.8, 9.8 Hz, H5'), 5.08 (1H, t, J= 9.7 Hz, H4'), 5.32 (1H, t, J=9.8 Hz, H2'), 5.75 (1H, t, J=13.2 Hz, H3'), 6.20 (1H, d, J = 10.4 Hz, H1'), 7.25 (1H, s, CH=C), 7.42-8.75 (12H, m, H$_{arom}$).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-methyl-2-thiohydantoin (14c): Yield 2.60 g (87%), mp 182°C. Anal. Calcd. for $C_{29}H_{30}N_2O_{10}S$: C, 58.19; H, 5.05; N, 4.68; Found: C, 58.40; H, 5.30; N, 5.10. EI MS *m/z* 598 (M^+). IR cm^{-1} (KBr) 1755 (OCO), 1722 (NCO). ^1H NMR (DMSO-d_6): δ 1.94, 1.98, 2.03, 2.06 (12H, 4s, 4Ac), 3.23 (3H, s, Me), 4.22 (1H, d, J= 4.1 Hz, H6'), 4.28 (2H, m, H5', H6''), 5.03 (1H, t, J = 9.8 Hz, H4'), 5.40 (1H, t, J = 9.7 Hz, H2'), 5.55 (1H, t, J= 8.8 Hz, H3'),5.82 (1H, d, J = 10.0 Hz, H1'), 7.00 (1H, s, CH=C), 7.19-8.17 (7H, m, H_{arom}).

(*Z*)-5-(2-Naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-phenyl-2-thiohydantoin (14d): Yield 2.90 g (88%), mp 179°C. Anal. Calcd. for $C_{34}H_{32}N_2O_{10}S$: C, 61.81; H, 4.88; N, 4.24; Found: C, 62.10; H, 5.20; N, 4.10. EI MS *m/z* 660 (M^+). IR cm^{-1} (KBr) 1758 (OCO), 1720 (NCO).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-gluco- and D-galactopyranosyl)-3-substituted-2-thiohydantoins (14e-h). To a solution of 2-thiohydantoins **11c,d** (5 mmol) in aqueous potassium carbonate (23.33%, 3 ml) was added a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-gluco- or D-galactopyranosyl bromide **4** (2.26 g, 5.5 mmol) in acetone (20 ml). The reaction mixture was stirred 12 h at room temperature until the starting material was consumed (TLC with ether-petroleum ether; 50: 50, v/v). The mixture was evaporated under reduced pressure at 40 °C and the residue was washed with distilled water to remove the potassium bromide formed. The solid product was dried and crystallized from absolute ethanol.

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-methyl-2-thiohydantoin (14e): Yield 2.30 g (75%), mp 180°C. Anal. Calcd. for $C_{29}H_{30}N_2O_{11}S$: C, 56.67; H, 4.92; N, 4.56; Found: C, 57.00; H, 5.10; N, 4.90. EI MS *m/z* 614 (M^+). IR cm^{-1} (KBr) 3500 (OH), 1760 (OCO), 1720 (NCO). ^1H NMR (DMSO-d_6): δ 1.70, 1.99, 2.03, 2.08 (12H, 4s, 4Ac), 4.07 (1H, d, J= 4.3 Hz, H6'), 4.23 (2H, m, H5', H6''), 5.12 (1H, t, J = 9.3 Hz, H4'), 5.35 (1H, d, J = 9.4 Hz, H2'), 5.50 (1H, t, J = 9.5 Hz, H3'),5.86 (1H, d, J = 10.3 Hz, H1'), 7.10 (1H, s, CH=C), 7.20-8.10 (6H, m, H_{arom}), 12.52 (1H, s, OH).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-phenyl -2-thiohydantoin (14f): Yield 2.60 g (77%), mp 177°C. Anal. Calcd.

for $C_{34}H_{32}N_2O_{11}S$: C, 60.35; H, 4.77; N, 4.14; Found: C, 60.10; H, 5.00; N, 4.90. EI MS *m/z* 676 (M^+). IR cm^{-1} (KBr) 3500 (OH), 1760 (OCO), 1722 (NCO).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-methyl-2-thiohydantoin (14g): Yield 2.60 g (87%), mp 182°C. Anal. Calcd. for $C_{29}H_{30}N_2O_{11}S$: C, 56.67; H, 4.92; N, 4.56; Found: C, 56.40; H, 5.30; N, 4.70. EI MS *m/z* 614 (M^+). IR cm^{-1} (KBr) 1755 (OCO), 1719 (NCO).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-2-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-3-phenyl-2-thiohydantoin (14h): Yield 2.50 g (74%), mp 190 °C. Anal. Calcd. for $C_{34}H_{32}N_2O_{11}S$: C, 60.35; H, 4.77; N, 4.14; Found: C, 60.70; H, 4.60; N, 4.40. EI MS *m/z* 676 (M^+). IR cm^{-1} (KBr) 3500 (OH), 1758 (OCO), 1719 (NCO). ^1H NMR (DMSO-d_6): δ 1.74, 1.98, 2.08, 2.13 (12H, 4s, 4Ac), 4.03 (1H, d, J= 4.5 Hz, H6'), 4.20 (2H, m, H5', H6''), 5.12 (1H, t, J = 9.3 Hz, H4'), 5.36 (1H, t, J = 9.4 Hz, H2'), 5.52 (1H, t, J = 9.3 Hz, H3'),5.88 (1H, d, J = 10.3 Hz, H1'), 7.08 (1H, s, CH=C), 7.20-8.10 (11H, m, H_{arom}), 12.62 (1H, s, OH).

(*Z*)-5-Naphthylmethylene-3-phenylhydantoins (15a,b). A mixture of **14b** (1.5 mmol) or **14f** (1.5 mmol) and concentrated hydrochloric acid (5 ml) in ethanol (20 ml) was heated under reflux for 2 h until the starting material was consumed (TLC with chloroform-methanol; 98: 2, v/v). The yellow solid, which separated, was collected and recrystallized from dimethylformamide.

(*Z*)-5-(2-Naphthylmethylene)-3-phenylhydantoin (15a): Yield 0.45 g (96%), mp 230°C. Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91; Found: C, 76.20; H, 4.30; N, 8.60. EI MS *m/z* 314 (M^+). IR cm^{-1} (KBr) 3290 (NH), 1760 (C_4O), 1717 (C_2O). ^1H NMR (DMSO-d_6): δ 6.86 (1H, s, CH=C), 7.42-8.05 (12H, m, H_{arom}), 12.80 (1H, s, N_1H).

(*Z*)-5-(2-Hydroxy-1-naphthylmethylene)-3-phenylhydantoin (15b): Yield 0.48 g (97%), mp 260°C. Anal. Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48; Found: C, 72.30; H, 4.00; N, 8.10. EI MS *m/z* 330 (M^+). IR cm^{-1} (KBr) 3294 (NH), 1765 (C_4O), 1718 (C_2O). ^1H NMR (DMSO-d_6): δ 7.07 (1H, s, CH=C), 7.28-7.90 (12H, m, H_{arom}), 10.52 (1H, s, N_1H), 11.86 (1H, s, OH).

Acknowledgment: The authors would like to express their gratitude and thanks to

Prof. Dr. Nils G. Johansson, Medicinal Chemistry, Medivir AB, Sweden, for carrying out the antiviral testing of the prepared compounds.

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Received November 7, 1995
Accepted September 25, 1996