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Note

Glycosylation of 2-thiohydantoin derivatives. Synthesis of some novel S-alkylated and S-glucosylated hydantoins

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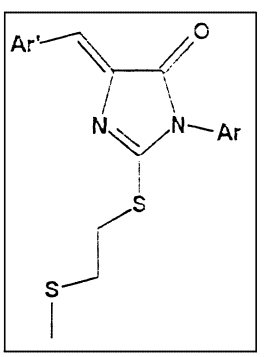
Abstract

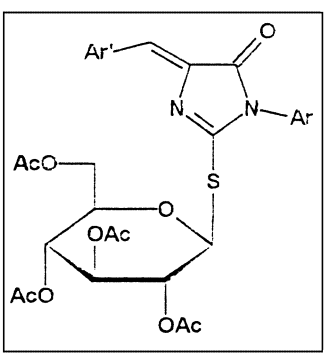
3-Aryl-5-((*Z*)-arylidene)-3-aryl-2-(2-methylthioethyl)-2-thiohydantoins **3a**–**f** and 3-aryl-5-((*Z*)-arylidene)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins **7a**–**n** were prepared from the reaction of 3-aryl-5-((*Z*)-arylidene)-2-thiohydantoins **2a**–**n** with methylthioethyl chloride or 2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl bromide via three different routes. The compounds did not display any antiviral and antitumoral activity. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: 3-Aryl-2-thiohydantoins; 3-Aryl-5-((*Z*)-arylidene)-2-(2-methylthioethyl)-2-thiohydantoins; 3-Aryl-5-((*Z*)-arylidene)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins; Antiviral; Antitumor agents

There has been much interest in the synthesis and properties of derivatives of 2-thiohydantoins which are useful synthetic intermediates and have also found applications as therapeutics[1–4] as well as fungicides and herbicides.[5] Furthermore, several 5-arylidene-3-aryl-2-thiohydantoins and their nucleosides show potent activity against the herpes simplex virus (HSV),[6] the human immunodeficiency virus (HIV)[7] and the leukaemia subpanel.[8] In addition, the biological activity of hydantoin and 2-thiohydantoin derivatives has been known for a long time. The hydantoin nucleus containing an urea moiety is responsible for a variety of biological activities such as antiarrhythmic,[9–11] antihypertensive,[12,13] antiviral,[14] antineoplastic,[15] anticonvulsant,[16] and antimycobacterial.[17] Hydantoins also exhibit platelet aggregation[18] and aldose reductase inhibition.[19,20] In the course of identifying new chemical structures which may serve as leads for designing novel antitumor and antiviral agents, we were particularly interested in 2-thiohydantoins. As part of our program directed towards new, simple and efficient procedures for the synthesis of antiviral and antitumor agents,[6–8] the linking of 3-aryl-5-arylidene-2-thiohydantoins to hydrophilic and lipophilic moieties such as D-glucose and methyl ethyl thioether was considered.



3a-f



7a-n

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Structures such as **3a**–**f** and **7a**–**n** were selected and their synthesis planned via the anticipated coupling of these two moieties by a thiol unit. Indeed the preparation of simpler analogs such as **3a**–**f** was first studied in order to test three synthetic pathways and the possible tautomeric equilibrium of such structures.

3-Aryl-5-((*Z*)-arylidene)-2-(2-methylthioethyl)-2-thiohydantoins **3a**–**f** and 3-aryl-5-((*Z*)-arylidene)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins **7a**–**n** were obtained via three different routes. 3-Aryl-2-thiohydantoins **1a**–**d** were reacted with the appropriate aromatic aldehydes by refluxing in a solution of anhydrous sodium acetate and glacial acetic acid to afford the corresponding 3-aryl-5-((*Z*)-arylidene)-2-thiohydantoins **2a**–**n**. The structures of **2a**–**n** were established and confirmed by their elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). Typically, the ^{1}H NMR spectrum of compound **2a** showed a singlet at δ 6.83 ppm assigned to a vinyl proton, indicating the *Z* configuration for the exocyclic double bond, in agreement with the ^{1}H NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoins whose vinyl protons appear at δ 6.10–6.35 and 6.40–6.75 ppm, respectively.[21,22] The ^{13}C NMR spectrum of compound **2a** showed a singlet at δ 108.00 ppm assigned to the vinyl carbon, indicating the *Z* configuration for the exocyclic double bond, in agreement with the ^{13}C NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoins whose vinyl carbons appear at δ 105–115 and 115–125 ppm, respectively.[21,22] Compounds **2a**–**f** were reacted with methylthioethyl chloride in ethanolic potassium hydroxide at room temperature to afford 3-aryl-5-((*Z*)-arylidene)-2-(2-methylthioethyl)-2-thiohydantoins **3a**–**f**. Compound **3a** was also synthesised via the condensation of 3-(4-bromophenyl)-2-thiohydantoin **1a** with benzaldehyde followed by the addition of methylthioethyl chloride. Also, compound **3a** was independently synthesised through another pathway via the condensation of 5-((*Z*)-benzylidene)-3-(4-bromophenyl)-2-(trimethylsilyl)-2-thiohydantoin (**4**), which in turn was prepared from the reaction of **2a** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in acetonitrile, followed by addition of methylthioethyl chloride and trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 70–80 °C for 1 h. The S-alkylated derivative **3a** was isolated by silica gel column chromatography in 72% yield and no other N-alkylated derivative **5** was detected in the reaction mixture (TLC). The structures of **3a**–**f** were established and confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The IR absorption spectra of compound **3c** was characterised by the absence of signal for NH at 3197 cm^{-1} and the presence of a signal at 1710 cm^{-1} due to the carbonyl group. The ^{1}H NMR spectrum of compound **3c** showed a singlet at δ 7.04 ppm assigned to the vinyl proton, indicating the *Z* configuration for the exocyclic double bond, in agreement with the ^{1}H NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoins whose vinyl protons appear at δ 6.10–6.35 and 6.40–6.75 ppm, respectively[21,22] and the ^{1}H NMR spectrum of its oxygen analogue **6**, which in turn was prepared from the reaction of **3c** with 12 N hydrochloric acid in refluxing ethanol. Its vinyl proton appeared at δ 6.75 ppm (Scheme 1).

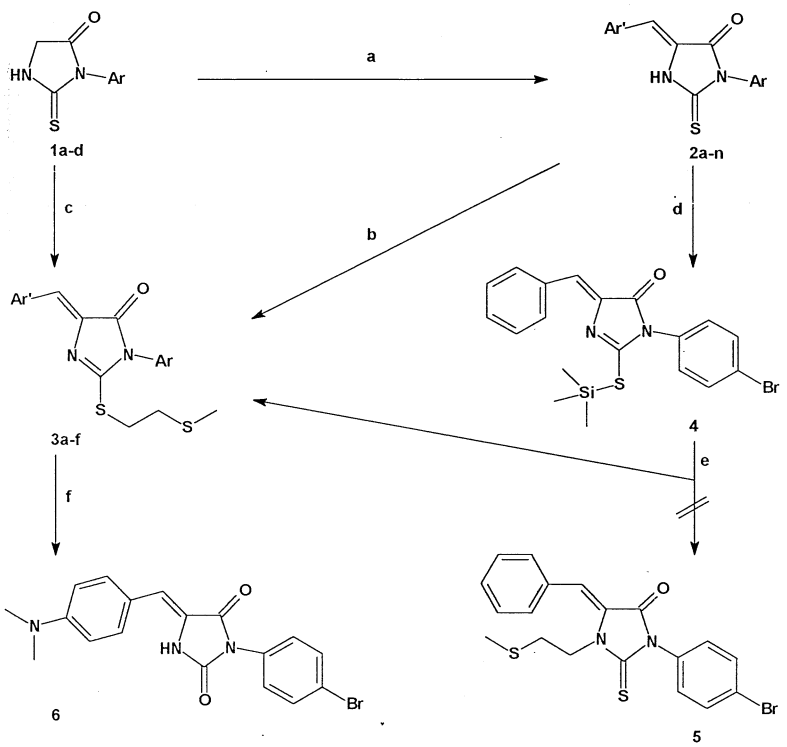
Compounds **2a**–**n** were reacted with 1.1 equivalents of NaH in anhydrous acetonitrile followed by 1.1 equivalents of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide to give 3-aryl-5-((*Z*)-arylidene)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiohydantoins **7a**–**n**. Compound **7a** was also independently synthesised by reaction of **1a** with benzaldehyde in the presence of ethanolic potassium hydroxide followed by evaporation of ethanol and reaction of the residue with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in aqueous acetone at room temperature. Compound **7a** was independently synthesised through another pathway via the condensation of **4** with 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranoside in the presence of TMSOTf at 70–80 °C for 1 h. The S-glucosylated derivative **7a** was isolated by silica gel (E. Merck) column chromatography in 58% yield. No N-glucosylated derivative **8** was detected in the reaction mixture (TLC). The structures of **7a**–**n** were established and confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The IR absorption spectrum of compound **7d** was characterised

by the absence of signal for NH at 3198 cm^{-1} and the presence of a signal at 1750, 1729 cm^{-1} due to the carbonyl groups. The ^1H NMR spectrum of compound **7d** showed a singlet at δ 7.70 ppm assigned to the vinyl proton, indicating the *Z* configuration for the exocyclic double bond, in agreement with the ^1H NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoins whose vinyl protons appear at δ 6.10–6.35 and 6.40–6.75 ppm, respectively.[21,22] The ^1H NMR spectrum of the oxygen analogue **9**, which in turn was prepared from the reaction of **7d** with sodium methoxide in methanol at room temperature, shows vinyl protons at δ 6.67 ppm. In agreement with the latter result, attempts to deprotect the S-glucosylated derivatives **7a**–**n** in methanolic sodium methoxide (Scheme 2) resulted in the recovery of the corresponding hydantoin.

Compounds **3a**–**f** and **7a**–**n** have been examined for antiviral and antitumoral properties. Both, even at 100 μg mL^{-1} did not inhibit HIV-1.[24] No antitumoral activity in the NCI in vitro disease-oriented human cells screening panel assay was found.[25,26]

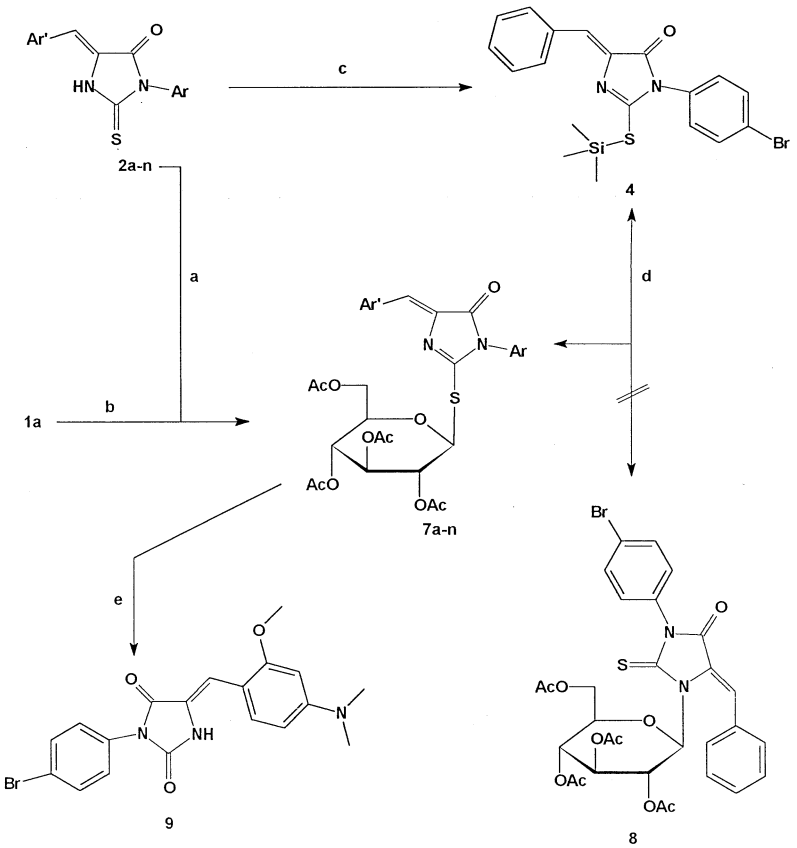
1. Experimental

^1H (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were measured on a Bruker Advance DPX 300 instrument using Me_4Si as



	Ar	Ar'		Ar	Ar'
1a	4-BrC_6H_4		**2i**	4-ClC_6H_4	C_6H_5
b	4-MeC_6H_4		**j**	4-ClC_6H_4	3,4-methylenedioxyphenyl
c	4-ClC_6H_4		**k**	4-ClC_6H_4	4-$Me_2NC_6H_4$
d	4-$Me_2NC_6H_4$		**l**	4-$Me_2NC_6H_4$	C_6H_5
2a	4-BrC_6H_4	C_6H_5	**m**	4-$Me_2NC_6H_4$	4-$Me_2NC_6H_4$
b	4-BrC_6H_4	3,4-methylenedioxyphenyl	**n**	4-$Me_2NC_6H_4$	2-thienyl
c	4-BrC_6H_4	4-$Me_2NC_6H_4$	**3a**	4-BrC_6H_4	C_6H_5
d	4-BrC_6H_4	2-MeO,4-$Me_2NC_6H_3$	**b**	4-BrC_6H_4	3,4-methylenedioxyphenyl
e	4-MeC_6H_4	C_6H_5	**c**	4-BrC_6H_4	4-$Me_2NC_6H_4$
f	4-MeC_6H_4	3,4-methylenedioxyphenyl	**d**	4-BrC_6H_4	2-MeO,4-$Me_2NC_6H_3$
g	4-MeC_6H_4	4-$Me_2NC_6H_4$	**e**	4-MeC_6H_4	C_6H_5
h	4-MeC_6H_4	2-thienyl	**f**	4-MeC_6H_4	3,4-methylenedioxyphenyl

Scheme 1. Reagents and conditions: (a) Ar′CHO, AcONa, AcOH, reflux. (b) KOH, EtOH, $H_3CSCH_2CH_2Cl$, rt (c) (i) Ar′CHO, KOH, EtOH, rt; (ii) $MeSCH_2CH_2Cl$, rt (d) CH_3CN, BSA, 70–80 °C. (e) $CH_3SCH_2CH_2Cl$, TMSOTf, 70–80 °C. (f) Conc HCl, EtOH.



	Ar	Ar'		Ar	Ar'
7a	4-BrC_6H_4	C_6H_5	**7h**	4-MeC_6H_4	2-thienyl
b	4-BrC_6H_4	3,4-methylenedioxyphenyl	**i**	4-ClC_6H_4	C_6H_5
c	4-BrC_6H_4	4-$Me_2NC_6H_4$	**j**	4-ClC_6H_4	3,4-methylenedioxyphenyl
d	4-BrC_6H_4	2-MeO,4-$Me_2NC_6H_3$	**k**	4-ClC_6H_4	4-$Me_2NC_6H_4$
e	4-MeC_6H_4	C_6H_5	**l**	4-$Me_2NC_6H_4$	C_6H_5
f	4-MeC_6H_4	3,4-methylenedioxyphenyl	**m**	4-$Me_2NC_6H_4$	4-$Me_2NC_6H_4$
g	4-MeC_6H_4	4-$Me_2NC_6H_4$	**n**	4-$Me_2NC_6H_4$	2-thienyl

Scheme 2. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, NaH, CH_3CN, rt (b) (i) Ar′CHO, KOH, EtOH, rt; (ii) MeCOMe, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, rt (c) CH_3CN, BSA, 70–80 °C. (d) 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose, 70–80 °C. (e) CH_3ONa, CH_3OH, rt

internal reference. Mass spectra were recorded on a Finnigan MAT-INCOS 500 spectrometer with ionisation by electron impact (70 eV). Melting points are uncorrected. Aluminum sheets coated with Silica Gel 60 F_{254} (E. Merck) were used for TLC. Detection was effected by viewing under a short wavelength UV lamp. IR spectra were measured on a Nicolet Magna 750. Column chromatography was performed with Silica Gel 60 mesh ASTM (E. Merck). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide was prepared according to the published method of Lemieux.[23]

3-Aryl-2-thiohydantoins (**1a–d**).—Glycine (0.75 g, 10 mmol) was dissolved in a mixture of water (25 mL) and pyridine (25 mL). The pH of the solution was adjusted to about 9 as shown by an indicator paper by the addition of 1 N NaOH. The solution was heated to 40 °C and kept at that temperature during the reaction. Aryl isothiocyanates (20 mmol) were added with vigorous stirring. Small portions of 1 N NaOH were added to keep the pH at about 9. The reaction was completed when the alkali consumption ceased (ca. 60 min). Pyridine and excess aryl isothiocyanate were then removed by repeated extraction with equal vol of benzene. Subsequently, conc HCl (3 mL) was added and the mixture was refluxed for 2 h. The reaction mixture was concentrated to half its volume under vacuum and cooled to rt. The pale yellow solid precipitate was col-

lected by filtration and recrystallised from MeOH to give the products **1a**–**d** (Tables 1 and 2).

3-Aryl-5-((Z)-arylidene)-2-thiohydantoins (**2a**–**n**).—To a mixture of 3-aryl-2-thiohydantoins **1a**–**d** (10 mmol), anhyd AcONa (2.32 g, 28.29 mmol) and glacial AcOH (15 mL) was added followed by the appropriate aromatic aldehyde (11 mmol). The mixture was heated under reflux for 4 h, cooled to rt and then poured into cold water. The yellow solid precipitate was collected by filtration and recrystallised from AcOH to give the products **2a**–**n** (Tables 1 and 2).

3-Aryl-5-((Z)-arylidene)-2-(2-methylthioethyl)-2-thiohydantoins (**3a**–**f**)

Method A. At rt, 5-((*Z*)-arylidene)-3-aryl-2-thiohydantoins **2a**–**f** (2 mmol) were dissolved in ethanolic KOH (2%, 7 mL). To this solution, methylthioethyl chloride (143 mg, 2.20 mmol) was added, and the reaction mixture was stirred for 12 h at rt. The yellow precipitated solid was collected by filtration and recrystallised from MeOH to give the products **3a**–**f** (Tables 1 and 2).

Method B. At rt, 3-(4-bromophenyl)-2-thiohydantoin (**1a**) (0.27 g, 1 mmol) was dissolved in ethanolic KOH (2%, 3.5 mL). To this solution was added benzaldehyde (0.12 g, 1.10 mmol) and the mixture was stirred for 12 h at rt. To this mixture was added methylthioethyl chloride (0.12 g, 1.10 mmol) and the mixture was again stirred at rt for 12 h. The precipitated solid was collected by filtration and recrystallised from EtOH to give the product **3a** (0.36 g, 84%), identical to the product found with method A.

Method C. Compound **2a** (0.36 g, 1 mmol) was suspended in anhyd MeCN (5 mL) and BSA (0.25 mL, 1 mmol) was added, and the reaction mixture was stirred at 70–80 °C for 30 min. Methylthioethyl chloride (0.11 g, 1 mmol) dissolved in anhyd MeCN (5 mL) was added to the reaction mixture via a canula. Finally TMSOTf (0.2 mL, 1 mmol) was added, and the reaction mixture was stirred at 70–80 °C for 1 h. Satd $NaHCO_3$ was added to quench the reaction and the resulting mixture was extracted with CH_2Cl_2. The combined organic fractions were washed with satd NaCl solution, dried over $MgSO_4$, filtered, and evaporated to dryness. The solid obtained was purified by flash chromatography (1:1, diethyl ether–petroleum ether, bp 40–60 °C) to give **3a** (0.31 g, 72%) identical to the product found with method A.

5-((Z)-4-Dimethylaminobenzylidene)-3-(4-bromophenyl)hydantoin (**6**).—To a solution of 5-((*Z*)-4-dimethyl-aminobenzylidene)-3-phenylmethyl-2-(2-methylthioethyl)-2-thiohydantoin (**3c**) (0.51 g, 1 mmol) in EtOH (10 mL) was added 12 N HCl (1 mL). The reaction mixture was refluxed for 2 h until the starting material was consumed (TLC) and cooled to rt. The separated solid was filtered off and recrystallised from AcOH to give **6** (0.30 g) (Tables 1 and 2).

3-Aryl-5-((Z)-arylidene)-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-2-thiohydantoins (**7a**–**n**)

Method A. At rt, 3-aryl-5-((*Z*)-arylidene)-2-thiohydantoins **2a**–**n** (1 mmol) were suspended in anhyd MeCN (5 mL). To this suspension was added NaH (60%, 45 mg, 1 mmol), and the mixture was stirred at rt for 30 min. The mixture became clear after 15 min. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.41 g, 1 mmol) was added, and the mixture was stirred at rt for 12 h until the starting material was consumed (TLC) and then filtered. The residue from the evaporation of the filtrate under reduced pressure was purified by flash chromatography (1:1, diethyl ether–petroleum ether, bp 40–60 °C) to give the products **7a**–**n** (Tables 1 and 2).

Method B. At rt 3-(4-bromophenyl)-2-thiohydantoin (**1a**) (0.27 g, 1 mmol) was dissolved in ethanolic KOH (2%, 3.5 mL). To this solution was added the benzaldehyde (0.12 g, 1.10 mmol) and the mixture was stirred for 12 h at rt. The solvent was evaporated to dryness under vacuum and the residue was dissolved in aq acetone (5 mL, 90%). To this mixture was added 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.41 g, 1 mmol). The reaction mixture was stirred for 6 h at rt until the starting material was consumed (TLC). The mixture was evaporated under reduced pressure at 40 °C and the residue was washed with distilled water to remove the NaBr formed. The solid product was collected by filtration, dried and recrystallised from abs EtOH to give the product **7a** (0.58 g, 84%) identical to the product found with method A.

Table 1
IR and ^{1}H NMR data for **1**–**9**

Compound	IR (KBr) (cm^{-1})	^{1}H NMR (Me_2SO, $CDCl_3$) (δ)
1a	3200 (NH), 1751 (C=O)	10.23 (s, 1 H, N-1 H), 7.52, 7.15 (2d, $J = 8.50$ Hz, 4 H, Ar), 4.13 (s, 2 H, H-5)
1b	3198 (NH), 1750 (C=O)	10.38 (s, 1 H, N-1 H), 7.51–7.34 (2d, $J = 8.45$ Hz, 4 H, Ar), 4.39 (s, 2 H, H-5)
1c	3198 (NH), 1752 (C=O)	7.45, 7.21 (2d, $J = 8.50$ Hz, 4 H, Ar), 7.18 (s, 1 H, N-1 H), 4.22 (s, 2 H, H-5)
1d	3196 (NH), 1754 (C=O)	10.14 (s, 1 H, N-1 H), 7.05, 6.75 (2d, $J = 8.60$ Hz, 4 H, Ar), 4.20 (s, 2 H, H-5), 3.00 (s, 6 H, NMe_2)
2a	3198 (NH), 1756 (C=O)	8.84 (s, 1 H, N-1 H), 7.70–7.24 (m, 9 H, Ar), 6.83 (s, H, =CH)
2b	3200 (NH), 1750 (C=O)	12.44 (s, 1 H, N-1 H), 8.10–6.90 (m, 7 H, Ar), 6.61 (s, 1 H, =CH), 6.06 (s, 2 H, OCH_2O)
2c	3197 (NH), 1755 (C=O)	12.22 (s, 1 H, N-1 H), 7.70–7.24 (m, 9 H, Ar), 6.83 (s, H, =CH), 3.00 (s, 6 H, NMe_2)
2d	3198 (NH), 1752 (C=O)	9.63 (s, 1 H, N-1 H), 6.18–7.63 (m, 8 H, =CH, Ar–H), 4.01 (s, 3 H, OMe), 3.08 (s, 6 H, NMe_2)
2e	3190 (NH), 1750 (C=O)	9.16 (s, 1 H, N-1 H), 7.50–7.24 (m, 9 H, Ar), 6.84 (s, 1 H, =CH), 2.42 (s, 3 H, Me)
2f	3196 (NH), 1757 (C=O)	12.44 (s, 1 H, N-1 H), 7.53–6.99 (m, 7 H, Ar), 2.35 (s, 3 H, Me), 6.61 (s, 1 H, =CH), 6.10 (s, 2 H, OCH_2O)
2g	3196 (NH), 1752 (C=O)	12.42 (s, 1 H, N-1 H), 8.20–6.70 (m, 8 H, Ar), 6.62 (s, 1 H, =CH), 3.00 (s, 6 H, NMe_2), 2.35 (s, 3 H, Me)
2h	3192 (NH), 1756 (C=O)	12.45 (s, 1 H, N-1 H), 7.57–7.15 (7 H, m, Ar), 6.90 (s, 1 H, =CH), 2.38 (s, 3 H, Me)
2i	3192 (NH), 1754 (C=O)	8.91 (s, 1 H, N-1 H), 7.50–7.20 (m, 9 H, Ar), 6.78 (s, 1 H, =CH)
2j	3192 (NH), 1755 (C=O)	8.80 (s, 1 H, N-1 H), 7.50–6.80 (m, 7 H, Ar), 6.70 (s, 1 H, =CH), 6.01 (s, 2 H, OCH_2O)
2k	3196 (NH), 1750 (C=O)	8.77 (s, 1 H, N-1 H), 7.50–6.76 (m, 9 H, =CH, Ar), 3.06 (s, 6 H, NMe_3)
2l	3192 (NH), 1752 (C=O)	8.90 (s, 1 H, N-1 H), 7.50–6.70 (m, 9 H, Ar), 6.78 (s, 1 H, =CH), 3.04 (s, 6 H, NMe_3)
2m	3198 (NH), 1756 (C=O)	11.86 (s, 1 H, N-1 H), 7.58, 7.07, 6.72, 6.64 (4d, $J = 9.00$ Hz, 8 H, Ar), 6.54 (s, 1 H, =CH), 2.90, 3.20 (s, 12 H, $2NMe_3$)
2n	3192 (NH), 1754 (C=O)	11.88 (s, 1 H, N-1 H), 8.00–6.75 (m, 9 H, =CH, Ar), 2.92 (s, 6 H, NMe_3)
3a	1708 (C=O)	8.18–7.20 (m, 9 H, Ar), 7.05 (s, 1 H, =CH), 3.54 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.96 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.25 (s, 3 H, SCH_3)
3b	1707 (C=O)	8.10, 7.61, 7.24, 6.70 (4d, $J = 8.50$ Hz, 8 H, Ar), 7.04 (s, 1 H, =CH), 3.53 (t, $J = 7.50$ Hz, 2 H, CH_2), 3.07 (s, 6 H, NMe_2), 2.97 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.26 (s, 3 H, SCH_3)
3c	1710 (C=O)	8.80–6.11 (m, 8 H, =CH, Ar), 3.89 (s, 3 H, OMe), 3.52 (2 H, t, $J = 7.50$ Hz, CH_2), 3.08 (s, 6 H, NMe_2), 2.97 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.25 (s, 3 H, SCH_3)
3d	1708 (C=O)	8.05–6.83 (m, 8 H, =CH, Ar), 6.03 (s, 2 H, OCH_2O), 3.54 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.96 (t, $J = 7.50$ Hz, 2 H, CH_2), 2.26 (s, 3 H, SCH_3)
3e	1707 (C=O)	8.20–7.19 (m, 9 H, Ar), 7.05 (s, 1 H, =CH), 3.54 (t, $J = 7.80$ Hz, 2 H, CH_2), 2.97 (t, $J = 7.80$ Hz, 2 H, CH_2), 2.42 (s, 2 H, Me), 2.26 (s, 3 H, SCH_3)
3f	1708 (C=O)	8.06–6.83 (m, 8 H, =CH, Ar), 6.02 (s, 2 H, OCH_2O), 3.52 (t, $J = 7.80$ Hz, 2 H, CH_2), 2.96 (2 H, t, $J = 7.80$ Hz, CH_2), 2.40 (s, 2 H, Me), 2.26 (s, 3 H, SCH_3)
6	3190 (NH), 1756 (C=O), 1708 (C=O)	10.70 (s, 1 H, N–1 H), 8.10, 7.60, 7.20, 6.70 (4d, $J = 8.50$ Hz, 8 H, Ar), 6.75 (s, 1 H, =CH), 2.96 (s, 6 H, NMe_2)
7a	1750 (Ac), 1730 (C=O)	7.18–8.18 (m, 9 H, Ar), 7.12 (s, 1 H, =CH), 5.82 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.40 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.26 (t, $J = 9.90$ Hz, 1 H, H-2′), 5.13 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.23–3.92 (m, 3 H, H-6′, H-5′), 2.08, 2.03, 2.02, 1.82 (3s, 12 H, 4Ac)

Table 1 (*Continued*)

Compound	IR (KBr) (cm^{-1})	^1H NMR (Me_2SO, $CDCl_3$) (δ)
7b	1750 (Ac), 1728 (C=O)	8.08–6.87 (m, 7 H, Ar), 7.04 (s, 1 H, =CH), 6.06 (s, 2 H, OCH_2O), 5.82 (d, $J = 10.20$ Hz, 1 H, H-1′), 5.40 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.26 (t, $J = 9.90$ Hz, 1 H, H-2′), 5.13 (t, $J = 9.90$ Hz, 1 H, H-4′), 4.32–3.92 (m, 3 H, H-6′, H-5′), 2.06, 2.04, 2.02, 1.90 (3s, 12H, 4Ac)
7c	1752 (Ac), 1727 (C=O)	8.08, 7.60, 7.20, 6.75 (4d, $J = 8.70$ Hz, 8 H, Ar), 7.09 (s, 1 H, =CH), 5.82 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.40 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.26 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.13 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.23–3.90 (m, 3 H, H-6′, H-5′), 3.11 (s, 6 H, NMe_3), 2.07, 2.02, 1.99, 1.85 (12 H, 3s, 4Ac)
7e	1752 (Ac), 1730 (C=O)	8.20–7.15 (m, 9 H, Ar), 7.11 (s, 1 H, =CH), 5.83 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.42 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.25 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.14 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.24–3.91 (m, 3 H, H-6′, H-5′), 2.41 (s, 3 H, CH_3), 2.09, 1.98, 1.94, 1.82 (4s, 12 H, 4Ac)
7f	1750 (Ac), 1730 (C=O)	6.88–8.11 (m, 8 H, =CH, Ar), 6.07 (s, 2 H, OCH_2O), 5.82 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.40 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.25 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.18 (t, $J = 9.75$ Hz, 1 H, 4′-H), 4.29–3.90 (m, 3 H, H-6′, H-5′), 2.41 (s, 3 H, CH_3), 2.08, 2.02, 1.98, 1.88 (4s, 12 H, 4Ac)
7g	1750 (Ac), 1729 (C=O)	8.20–6.90 (m, 9 H, =CH, Ar), 5.84 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.43 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.24 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.18 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.28–3.91 (m, 3 H, H-6′, H-5′), 3.15 (s, 6 H, NMe_2), 2.42 (s, 3 H, CH_3), 2.08, 2.04, 2.02, 1.89 (4s, 12 H, 4Ac)
7h	1750 (Ac), 1729 (C=O)	8.20–6.90 (m, 9 H, =CH, Ar), 5.84 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.43 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.24 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.18 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.28–3.91 (m, 3 H, H–6′, H-5′), 3.15 (s, 6 H, NMe_2), 2.42 (s, 3 H, CH_3), 2.08, 2.04, 2.02, 1.89 (4s, 12 H, 4Ac)
7i	1752 (Ac), 1727 (C=O)	8.12–7.18 (m, 9 H, =CH, Ar), 7.07 (s, 1 H, =CH), 5.78 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.43 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.24 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.08 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.18–3.86 (m, 3 H, H-6′, H-5′), 2.03, 1.97, 1.95, 1.76 (4s, 12 H, 4Ac)
7j	1751 (Ac), 1729 (C=O)	8.08–6.87 (m, 8 H, =CH, Ar), 6.06 (s, 2 H, OCH_2O), 5.80 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.40 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.22 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.15 (t, $J = 9.75$ Hz, 1 H, H–4′), 4.32–3.93 (m, 3 H, 6′-H, 5′-H), 2.09, 2.05, 2.01, 1.89 (4s, 12 H, 4Ac)
7k	1750 (Ac), 1731 (C=O)	8.09–6. 75 (m, 9 H, =CH, Ar), 5.80 (d, $J = 10.20$ Hz, 1 H, H-1′), 5.41 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.27 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.14 (t, $J = 9.90$ Hz, 1 H, H-4′), 4.24–3.90 (m, 3 H, H-6′, H-5′), 3.12 (s, 6 H, NMe_2), 2.08, 2.04, 2.02, 1.86 (4s, 12 H, 4Ac)
7l	1751 (Ac), 1730 (C=O)	8.18–6.74 (m, 10 H, =CH, Ar), 5.82 (d, $J = 10.20$ Hz, 1 H, H-1′), 5.38 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.24 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.13 (t, $J = 9.60$ Hz, 1 H, H-4′), 4.23–3.92 (m, 3 H, H-6′, H-5′), 3.01 (s, 6 H, NMe_2), 2.08, 2.04, 2.00, 1.82 (4s, 12 H, 4Ac)
7m	1750 (Ac), 1727 (C=O)	8.00–6.70 (m, 9 H, =CH, Ar), 5.80 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.38 (t, $J = 9.30$ Hz, 1 H, H-3′), 5.23 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.14 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.24–3.90 (m, 3 H, H-6′, H-5′), 3.20, 3.00 (2s, 12 H, $2NMe_2$), 2.08, 2.04, 2.02, 1.85 (4s, 12 H, 4Ac)
7n	1752 (Ac), 1728 (C=O)	8.02–6.68 (m, 9 H, =CH, Ar), 5.82 (d, $J = 10.50$ Hz, 1 H, H-1′), 5.36 (t, $J = 9.15$ Hz, 1 H, H-3′), 5.24 (t, $J = 9.75$ Hz, 1 H, H-2′), 5.13 (t, $J = 9.75$ Hz, 1 H, H-4′), 4.25–3.90 (m, 3 H, H-6′, H-5′), 3.09 (s, 6 H, $2NMe_2$), 2.08, 2.05, 2.02, 1.83 (4s, 12 H, 4Ac)
9	1757, 1707 (2 C=O)	10.70 (s, 1 H, N-1 H), 8.00–6.24 (m, 8 H, =CH, Ar), 3.83 (s, 3 H, OCH_3), 2.91 (s, 6 H, NMe_2)

Method C. Compound **2a** (0.36 g, 1 mmol) was suspended in anhyd MeCN (5 mL) and BSA (0.25 mL, 1 mmol) was added, and the reaction mixture was stirred at rt for 30 min. 1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose (0.39 g, 1 mmol) dissolved in anhyd MeCN (5 mL) was added to the reaction mixture via a canula. Finally TMSOTf (0.2 mL, 1 mmol) was added, and the reaction mixture was heated under reflux for 1 h. Satd $NaHCO_3$ was added to quench the reaction and the resulting mixture was extracted with CH_2Cl_2. The combined organic fractions were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to dryness. The solid obtained was purified by flash chromatography (1:1, diethyl ether–petroleum ether, bp 40–60 °C) to give 0.40 g

Table 2
Melting points, yields and analytical data for **1**–**9**

Compound	Melting point (°C)	Yield (g %)	Molecular formula (MW)	Found/Calculated (%)			M^+ (m/z)
				C	H	N	
1a	246	2.33, 86	$C_9H_7BrN_2OS$ (271)	40.0/39.9	2.8/2.6	10.3/10.3	271
1b	250	1.90, 92	$C_{10}H_{10}N_2OS$ (206)	58.0/58.2	5.2/4.9	13.5/13.6	206
1c	227	1.92, 85	$C_9H_7ClN_2OS$ (226)	47.9/47.7	3.4/3.1	12.1/12.4	226
1d	217	1.83, 78	$C_{11}H_{13}N_3OS$ (235)	55.9/56.2	5.7/5.6	17.6/17.9	235
2a	256	3.02, 84	$C_{16}H_{11}BrN_2OS$ (359)	53.2/53.5	3.3/3.1	08.0/07.8	359
2b	272	3.75, 93	$C_{17}H_{11}BrN_2O_3S$ (403)	50.2/50.6	3.0/2.7	06.8/06.9	403
2c	284	3.46, 86	$C_{18}H_{16}BrN_3OS$ (402)	53.5/53.7	4.3/4.0	10.3/10.4	402
2d	227	3.97, 92	$C_{19}H_{18}BrN_3O_2S$ (432)	52.6/52.8	4.3/4.2	09.5/09.7	432
2e	187	2.76, 94	$C_{17}H_{14}N_2OS$ (294)	69.6/69.4	4.8/4.8	09.3/09.5	294
2f	232	3.21, 95	$C_{18}H_{14}N_2O_3S$ (338)	63.5/63.9	4.0/4.2	08.1/08.3	338
2g	137	3.24, 96	$C_{19}H_{19}N_3OS$ (337)	67.9/67.6	5.8/5.7	12.8/12.5	337
2h	262	2.94, 98	$C_{15}H_{12}N_2OS_2$ (300)	59.7/60.0	3.8/4.0	09.7/09.3	300
2I	255	2.86, 91	$C_{16}H_{11}ClN_2OS$ (314)	60.7/61.0	3.7/3.5	03.5/08.9	314
2j	277	3.29, 92	$C_{17}H_{11}ClN_2O_3S$ (358)	56.6/56.9	3.3/3.1	07.5/07.8	358
2k	282	3.00, 84	$C_{18}H_{16}ClN_3OS$ (357)	60.6/60.4	4.8/4.5	11.5/11.7	357
2l	259	2.65, 82	$C_{18}H_{17}N_3OS$ (323)	66.4/66.8	5.6/5.3	12.9/13.0	323
2m	266	3.37, 92	$C_{20}H_{22}N_4OS$ (366)	65.3/65.5	6.4/6.1	15.2/15.3	366
2n	252	2.76, 84	$C_{16}H_{15}N_3OS_2$ (329)	58.1/58.3	4.9/4.6	12.5/12.8	329
3a	173	0.66, 76	$C_{19}H_{17}BrN_2OS_2$ (433)	52.3/52.7	4.3/4.0	06.3/06.5	433
3b	147	0.78, 82	$C_{21}H_{22}BrN_3OS_2$ (476)	52.5/52.9	4.9/4.7	08.7/08.8	476
3c	178	0.87, 86	$C_{22}H_{24}BrN_3O_2S_2$ (506)	52.3/52.2	5.0/4.8	08.2/08.3	506
3d	176	0.70, 73	$C_{20}H_{17}BrN_2O_3S_2$ (477)	49.9/50.3	3.8/3.6	05.7/05.9	477
3e	142	0.58, 79	$C_{20}H_{20}N_2OS_2$ (368)	64.9/65.2	5.8/5.5	07.4/07.6	368
3f	163	0.66, 80	$C_{21}H_{20}N_2O_3S_2$ (412)	61.3/61.1	5.2/4.9	06.7/06.8	412
6	307	0.30, 78	$C_{18}H_{16}BrN_3O_2$ (386)	55.7/56.0	4.5/4.2	10.8/10.9	386
7a	175	0.55, 80	$C_{30}H_{29}BrN_2O_{10}S$ (689)	52.0/52.3	4.3/4.2	03.8/04.1	689
7b	202	0.57, 78	$C_{31}H_{29}BrN_2O_{12}S$ (733)	50.6/50.8	4.3/4.0	03.9/03.8	733
7c	213	0.55, 75	$C_{32}H_{34}BrN_3O_{10}S$ (732)	52.2/52.5	4.8/4.7	05.4/05.7	732
7d	222	0.62, 81	$C_{33}H_{36}BrN_3O_{11}S$ (762)	52.3/52.0	4.8/4.8	05.2/05.5	762
7e	196	0.45, 72	$C_{31}H_{32}N_2O_{10}S$ (624)	59.5/59.6	5.5/5.2	04.2/04.5	624
7f	195	0.60, 90	$C_{32}H_{32}N_2O_{12}S$ (668)	57.4/57.5	5.1/4.8	04.0/04.2	668
7g	185	0.50, 75	$C_{33}H_{37}N_3O_{10}S$ (667)	59.1/56.4	5.5/5.6	06.2/06.3	667
7h	212	0.46, 73	$C_{29}H_{30}N_2O_{10}S_2$ (630)	55.0/55.2	4.9/4.8	04.104.4	630
7i	192	0.48, 74	$C_{30}H_{29}ClN_2O_{10}S$ (645)	59.5/55.9	4.7/4.5	04.2/04.3	645
7j	207	0.55, 80	$C_{31}H_{29}ClN_2O_{12}S$ (689)	53.7/54.0	4.4/4.2	03.8/04.1	689
7k	208	0.65, 94	$C_{32}H_{34}ClN_3O_{10}S$ (688)	55.6/55.9	5.4/5.0	05.9/06.1	688
7l	156	0.54, 83	$C_{32}H_{35}N_3O_{10}S$ (653)	58.7/58.8	5.5/5.4	06.2/06.4	653
7m	148	0.60, 86	$C_{34}H_{40}N_4O_{10}S$ (696)	58.3/58.6	5.6/5.8	08.3/08.0	696
7n	196	0.52, 79	$C_{30}H_{33}N_3O_{10}S_2$ (659)	54.2/54.6	5.3/5.0	06.1/06.4	659
9	250	0.20, 48	$C_{19}H_{18}BrN_3O_3$ (416)	54.6/54.8	4.7/4.4	10.3/10.1	416

(58%) of **7a** identical to the product found with method A.

5-((Z)-4-Dimethylamino-2-methoxybenzylidene)-3-(4-bromophenyl)hydantoin (**9**).—A mixture of the protected nucleoside **7d** (0.38 g, 0.5 mmol) in 10 mL of anhyd CH_3OH and 2.5 mL of 1% CH_3ONa was stirred at rt for 12 h. The separated solid was filtered off and recrystallised from AcOH to give **9** (0.20 g) (Tables 1 and 2).

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References

[1] Mehta, N.; Risinger, C. A.; Soroko, F. E. *J. Med. Chem.* **1981**, *24*, 465–468.
[2] Wessels, F. L.; Schwan, T. J.; Pong, S. F. *J. Pharm. Sci.* **1980**, *69*, 1102–1104.
[3] Bharucha, K. R.; Pavilinis, V.; Ajdukovic, D.; Shrenk, H. M., *Ger. Offen.* 2,329,745 **1974**; *Chem. Abstr.* **1974**, *80*, 95948d.
[4] Caldwell, A. G.; Harris, C. J.; Stepney, R.; Wittaker, N. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 495–505.
[5] Cremlyn, R. J.; Elias, R. S.; Geoghagan, M. J. A.; Braunholtz, J. T. *Brit.* **1964**, *166*, 967–974; *Chem. Abstr.* **1965**, *62*, 7768g.
[6] El-Barbary, A. A.; Khodair, A. I.; Pedersen, E. B.; Nielsen, C. *J. Med. Chem.* **1994**, *37*, 73–77.
[7] Khodair, A. I.; El-Subbagh, H. I.; El-Emam, A. A. *Boll. Chim. Farm.* **1997**, *136*, 561–567.
[8] Al-Obaid, A. A.; El-Subagh, H. I.; Khodair, A. I.; El-mazar, M. M. A. *Anti-Cancer Drugs* **1996**, *7*, 873–880.
[9] Havera, H. J.; Strycker, W. G. *US Patent* 3,994,904; **1976**; *Chem. Abstr.* **1977**, *86*, 106586m.
[10] Somma, A.; Mazzeo, V.; Matera, M. G.; Alfano, C.; Paone, G.; Scognamiglio, M.; Marmo, E. *Riv. Eru. Sci. Med. Farmacol.* **1981**, *3*, 269–276.
[11] Vidrio, H.; Mena, M. A.; Hong, E. *Arzneim. Forsch.* **1980**, *30*, 12–17.
[12] Blaha, L.; Weichet, J. *Czech. Patent* 151,744; **1974**; *Chem. Abstr.* **1974**, *81*, 63633b.
[13] Warner-Lambert, C. *US Patent* 4,452,798A; **1984**; *Chem. Abstr.* **1985**, *101*, 38476b.
[14] Bharucha, K. R.; Pavilanis, V.; Ajdukovic, D.; Shrenk, H.M. *Ger. Offen.* 2,329,745; **1974**; *Chem. Abstr.* **1974**, *80*, 95948d.
[15] Peng, G. W.; Marquez, V. E.; Driscroll, J. S. *J. Med. Chem.* **1975**, *18*, 846–849.
[16] Cortes, S.; Liao, Z. K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601–606.
[17] Zaidi, S. M. M.; Satsangi, R. K.; Nasir, P.; Agarwal, R.; Tiwari, S. S. *Pharmazie* **1980**, *35*, 755–756.
[18] Barraclough, P.; Caldwell, A. G.; Harris, C. J.; Jackson, W. P.; Whitte, B. J. R. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1815–1821.
[19] Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1988**, *31*, 230–243.
[20] Rizzi, J. P.; Schnur, R. C.; Hutson, N. J.; Kraus, K. G.; Kelbaugh, P. R. *J. Med. Chem.* **1989**, *32*, 1208–1213.
[21] Tan, S. F.; Ang, K. P.; Fong, Y. F. *J. Chem. Soc.,Perkin Trans.2* **1986**, 1941–1944.
[22] El–Barbary, A. A.; Khodair, A. I.; Pedersen, E. B. *J. Org. Chem.* **1993**, *58*, 5994–5999.
[23] Lemieux, R. U. *Methods Carbohydr. Chem.* **1963**, *2*, 221–222.
[24] Weislow, O. W.; Kiser, R.; Fine, D.; Bader, J.; Skoemaker, R. H.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 577–586.
[25] Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Poull, K.; Vistica, D.; Hose, C.; Langly, J.; Cronise, P.; Viagro-Wolff, A.; Gray-Goodrish, M.; Compell, H.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.
[26] Boyd, M. R.; Poull, K. D. *Drug Dev. Res.* **1995**, *34*, 91–109.