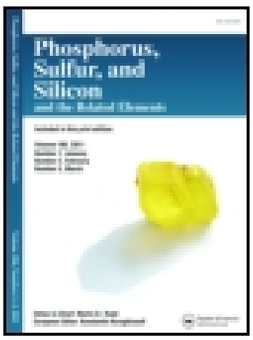


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

# A Convenient Preparation of 2-(2-Arylidene)- and 2-(2-Polyhydroxyalkylidene)hydrazono-4-imidazolidinones with Various Heterocyclic Side Chain Substituents at Position 5 as Potential Antiviral and Antitumor Agents

Ahmed I. Khodair

**To cite this article:** Ahmed I. Khodair (2002) A Convenient Preparation of 2-(2-Arylidene)- and 2-(2-Polyhydroxyalkylidene)hydrazono-4-imidazolidinones with Various Heterocyclic Side Chain Substituents at Position 5 as Potential Antiviral and Antitumor Agents, Phosphorus, Sulfur, and Silicon and the Related Elements, 177:5, 1157-1173, DOI: 10.1080/10426500211714

**To link to this article:** http://dx.doi.org/10.1080/10426500211714

Published online: 27 Oct 2010.

*Phosphorus, Sulfur and Silicon*, 2002, Vol. 177:1157–1173

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290092442



# A CONVENIENT PREPARATION OF 2-(2-ARYLIDENE)- AND 2-(2-POLYHYDROXYALKYLIDENE)HYDRAZONO-4-IMIDAZOLIDINONES WITH VARIOUS HETEROCYCLIC SIDE CHAIN SUBSTITUENTS AT POSITION 5 AS POTENTIAL ANTIVIRAL AND ANTITUMOR AGENTS

*Ahmed I. Khodair*
*Chemistry Department, Faculty of Education, Tanta University, Kafr El-Sheikh Branch, Kafr El-Sheikh, Egypt*

(Received September 24, 2001; accepted November 30, 2001)

*A variety of novel 5-[(*Z*)-arylidene]-2-[(2-(*E*)-arylidene)hydrazono]-4-imidazolidinones* ***1a–c*** *to* ***4a,b*** *and 5-[(*Z*)-arylidene]-2-[(2-(*E*)-polyhydroxyalkylidene)hydrazono]-4-imidazolidinones* ***5a–c*** *to* ***7a–c*** *were prepared from the reaction of 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins* ***8a–c*** *with 2-(*E*)-arylidene hydrazones* ***13a–d*** *and/or 2-(*E*)-monosaccharides hydrazones* ***16a–c****. The linear structure, and not that of the angular isomer, has been selected for the products. This structure has been confirmed from a model study of the condensation of 5-[(*Z*)-2-thienylidene]-2-hydrazono-4-imidazolidinone* ***9a*** *with benzaldehyde and* D*-galactose, respectively. The acetylation and benzoylation reactions of compounds* ***1–7*** *have been studied. All the new compounds were tested for their potential antiviral and antitumor activities.*

*Keywords:* Antitumor agents; antiviral; 2-(*E*)-Monosaccharides hydrazones; 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins; 5-[(*Z*)-(arylidene]-2-[(2-(*E*)-polyhydroxyalkylidene)hydrazono]-4-imidazolidinones

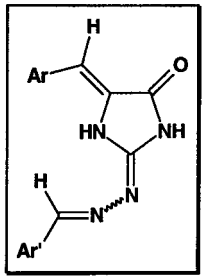
Present address Fakultät für Chemie, Universität Konstanz, Fach M 725, D-78457 Konstanz, Germany.

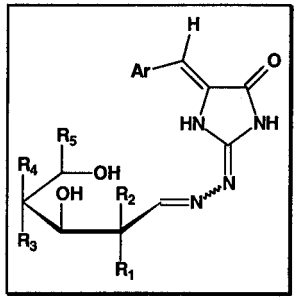
The author expresses gratitude and thanks to Professor John P. Bader, Antiviral Evaluation Branch and Professor V. L. Narayanan, Drug Synthesis and Chemistry Branch, National Cancer Institute, USA for carrying out the antiviral and antitumor screening.

Address correspondence to A. I. Khodair, Department of Chemistry, Faculty of Education, Tanta University, Kafr El-Sheikh, Egypt. E-mail: khodair_62@yahoo.com

## INTRODUCTION

In continuation of the study on the synthesis of 2-hydrazono-4-imidazolidinones[1,2] the convenient syntheses of new hydrazonoimidazolidinones with various heterocyclic side chains substituents at position 5 as potential antiviral and antitumor activities are reported. Substituted 4-imidazolidinones at C-5 are associated with a wide range of biological properties, including anticonvulsant,[3] antiviral,[5–7] antitumor,[8] and platelet inhibitory activities.[9] Furthermore, introduction of a furan-2-yl or thien-2-yl groups on to the position 5 of 2′-deoxyuridine afforded compounds with marked activity against HSV-1.[10,11] In this respect, it seemed worthwhile to link the imidazolidinone to an hydrophilic moiety such as a glycoside. It was thus anticipated that these heterocycles would posses better water solubility and an improved selectivity toward cancer cells which are known to be specifically enriched in carbohydrate receptors such as lectins.[12]




**1a-c:** Ar' = Ph
**2a-c:** Ar' = 2-thienyl
**3a-c:** Ar' = 3-indolyl
**4a,b:** Ar' = 2-furyl

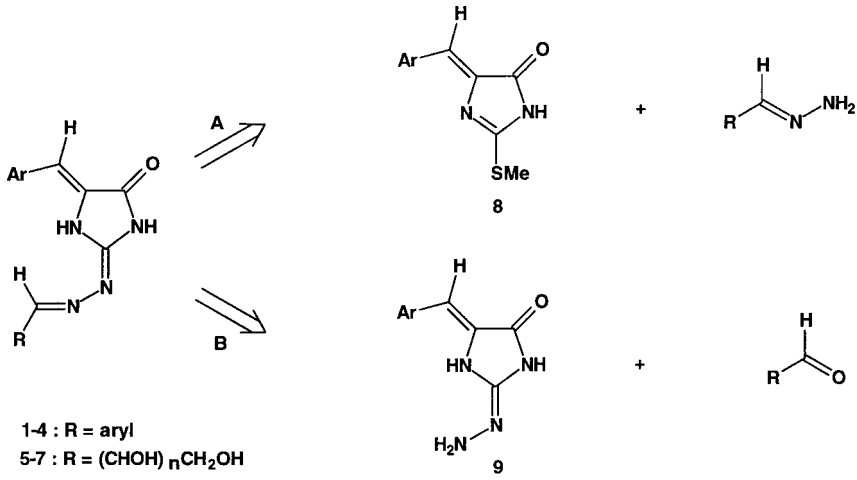
**a:** Ar = 2-thienyl
**b:** Ar = 2-furyl
**c:** Ar = 3-indolyl

**5a-c** = *D*-galacto
**6a-c** = *D*-manno
**7a-c** = *L*-arabino

Structures such as **5a–c** to **7a–c** were selected and their synthesis planned via the anticipated coupling of these two moieties by an azine unit. Indeed the preparation of simpler analogs such as **1a–c** to **4a**,**b** was first studied in order to test two synthetic pathways (vide infra) and the possible tautomeric equilibrium of such structures (notwithstanding the two azine isomers). Moreover, a number of 2-(alkylidenehydrazono)-4-imidazolidinone derivatives have been found to be useful inhibitors of the Maillard reaction in vitro and, as such, are potentially useful in the treatment of diseases caused by this reaction such as disorders associated with diabetes and aging. They also have hypoglycemic activity,

and are characterized by a long-lasting activity, excellent adsorption properties, low toxicity, and high stability.[13,14]

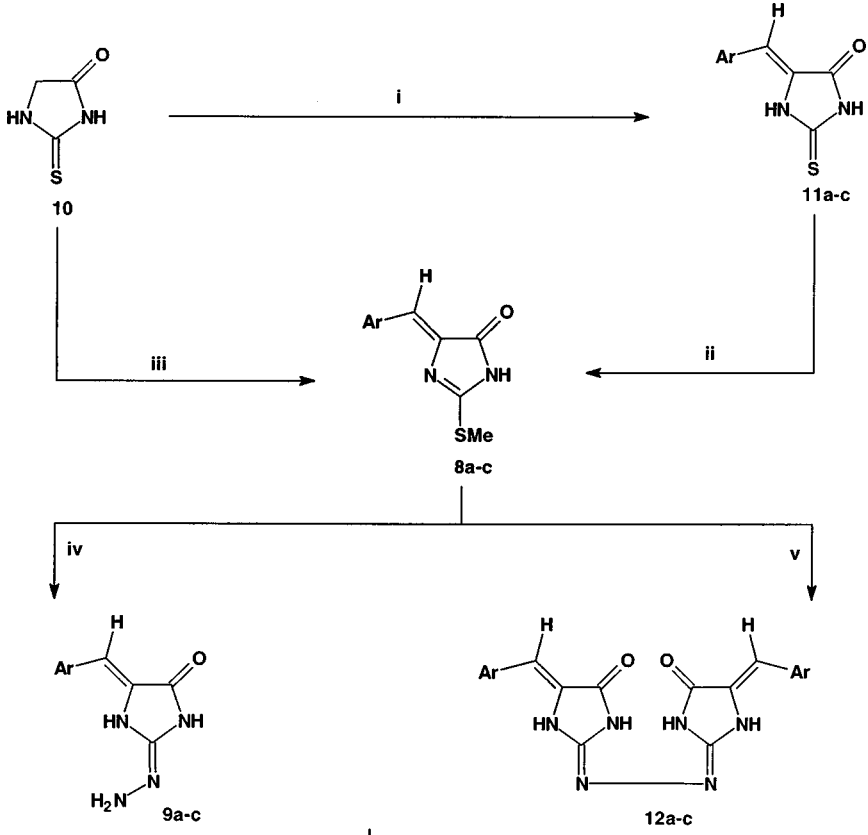
Retrosynthetic analysis shows that arylazinoimidazolidinones **1–7** could be prepared using two different strategies (Scheme 1). Path A relies on the condensation of an aldehyde hydrazone with methylthio derivative 8. These steps are inverted in path B which is based on the condensation of an aldehyde with an imidazolohydrazine **9**, which may be prepared from the reaction of the already mentioned methylthio derivative **8** with hydrazine hydrate.




**SCHEME 1**

## RESULTS AND DISCUSSION

The present work describes the synthesis, conformational analysis, and biological testing of a new series of 5-[(*Z*)-arylidene]-2-[(2-(*E*)-arylidene]hydrazono)-4-imidazolidinones **1a–c** to **4a**,**b** and 5-[(*Z*)-arylidene]-2-[(2-(*E*)-polyhydroxyalkylidene]hydrazono)-4-imidazolidinones **5a–c** to **7a–c** via two different routes. The condensation of aromatic aldehydes with 2-thiohydantoin **10** by stirring in a solution of piperidine and anhydrous ethanol afforded 5-[(*Z*)-arylidene]-2-thiohydantoins **11a–c**, which on methylation gave the corresponding 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins **8a–c** (Scheme 2). In our hands these compounds could be conveniently prepared in one pot by the reaction of compound **10** with aromatic



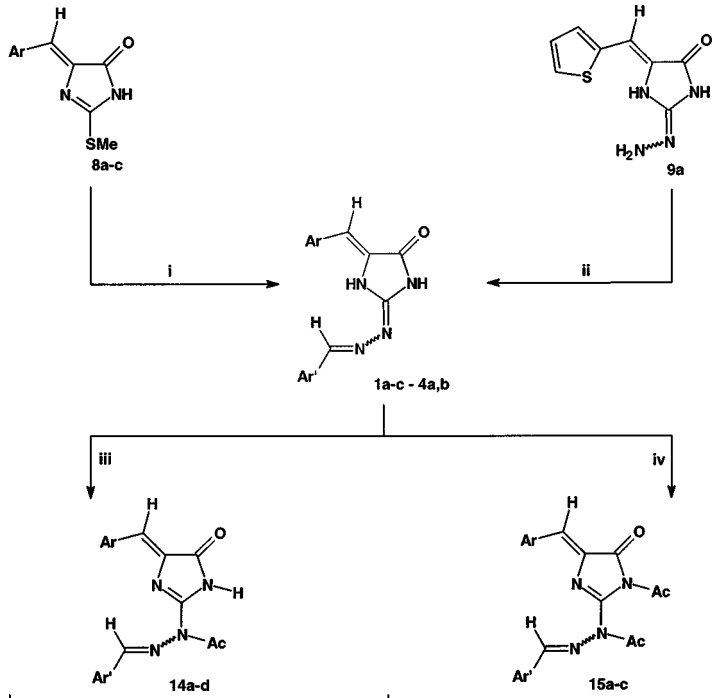

| 8-12 | Ar |
|---|---|
| a | 2-thienyl |
| b | 2-furyl |
| c | 3-indolyl |

**SCHEME 2** Reagents and conditions: (i) ArCHO, piperidine, EtOH, r.t.; (ii) NaOH, MeOH, MeI, r.t.; (iii) ArCHO, KOH, MeOH, stirring 12 h, r.t., MeI, stirring 6 h; (iv) $NH_2NH_2.H_2O$, EtOH, reflux; (v) $NH_2NH_2.H_2O$, AcOH, reflux.

aldehydes in presence of potassium hydroxide, followed by the addition of iodomethane at room temperature. When compounds **8a–c** were heated with hydrazine hydrate in boiling anhydrous ethanol until the evolution of methanethiol could not be detected, the corresponding 5-[(*Z*)-arylidene]-2-hydrazono-4-imidazolidinones **9a–c** were obtained in low yields. On the other hand, when compounds **8a–c** were heated with hydrazine hydrate in boiling acetic acid until the evolution of methanethiol could not be detected, the *N*,*N*-bis-(5-(*Z*)-arylidene-4-oxo-2-imidazolidinylidene)hydrazines **12a–c** were obtained in quantitative

yields. The structures of **9a–c** and **12a–c** were assigned on the basis of elemental analysis and spectral data (IR, $^1$H NMR, $^{13}$C NMR and MS). The IR absorption spectrum of compound **9a** was characterized by the presence of signals for the $NH_2$ and NH groups at 3312 and 3157 $cm^{-1}$ respectively, in addition to the carbonyl group at 1722 $cm^{-1}$. While the IR absorption spectrum of compound **12a** was characterized by the absence of a signal for the $NH_2$ group at 3312 $cm^{-1}$, the presence of a signal at 1718 $cm^{-1}$ due to the carbonyl group was found, in addition to the NH group at 3198 $cm^{-1}$. The $^1$H NMR spectra of compounds **9a** and **12a** showed a signals at $\delta$ 6.74, 6.75 assigned to the vinylic protons, indicating the presence of a *Z*-configurations for the exocyclic double bond, in agreement with the $^1$H NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoin derivatives whose vinyl protons appear at $\delta$ 6.10–6.35 and $\delta$ 6.40–6.75[15–17] respectively (Scheme 2).

As path B gives compounds **9a–c** in low yields, we turned attention to the use of the aldehyde hydrazones according to path A. Thus, 2-(*E*)-arylidene hydrazones **13a–d** were prepared following the method of Lock[18] via the reaction of hydrazine hydrate and aromatic aldehydes in ethanol at room temperature. Compounds **13a–d** were condensed with 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins **8a–c** to give 5-[(*Z*)-arylidene]-2-[(2-(*E*)-arylidene]hydrazono)-4-imidazolidinones **1a–c** to **4a**,**b** respectively. Compound **1a** was also independently synthesized through another pathway via the condensation of **9a** with the benzaldehyde in refluxing ethanol for 12 h (54%). The structures of **1a–c** to **4a**,**b** were established on the basis of their elemental analyses and spectral data (IR, $^1$H NMR, $^{13}$C NMR, and MS). The IR absorption spectrum of compound **1a** was characterised by the presence of a signal for the NH group at 3142 $cm^{-1}$, in addition to the carbonyl group at 1728 $cm^{-1}$. The singlet observed at $\delta$ 6.75 for the corresponding vinylic proton is in agreement with a *Z*-configuration of the double bond and this is confirmed by the $^{13}$C NMR spectrum which showed a singlet at 106.09 ppm. The corresponding carbon [$(CD_3)_2SO$] for 5-(*Z*)- and 5-(*E*)-arylidenehydantoin derivatives give signals at 105–113 ppm and 113–120 ppm,[15–17] respectively (Scheme 3). Treatment of compounds **1a–c** and **4a** with acetic anhydride in pyridine at room temperature gave 5-[(*Z*)-arylidene]-2-(1-acetyl-2-(*E*)-arylidenehydrazono)-4-imidazolidinones **14a–d**. The structures of **14a–d** were established on the basis of their elemental analyses and spectral data (IR, $^1$H NMR, $^{13}$C NMR, and MS). The IR absorption spectrum of compound **14a** was characterized by the presence of a signal for the acetoxy carbonyl group at 1752 $cm^{-1}$, in addition to the carbonyl group at 1727 $cm^{-1}$. The $^1$H NMR spectrum of compound **14a** showed a singlet at $\delta$ 6.82 assigned to the vinyl proton, indicating the presence of a *Z*-configuration




| | Ar' | Ar | | Ar' | Ar |
|---|---|---|---|---|---|
| **1a-c** | Ph | **a:** 2-thienyl | **14a** | Ph | 2-thienyl |
| **2a-c** | 2-thienyl | **b:** 2-furyl | **b** | Ph | 2-furyl |
| **3a-c** | 3-indolyl | **c:** 3-indolyl | **c** | Ph | 3-(1-acetylindolyl) |
| **4a,b** | 2-furyl | | **d** | 3-(1-acetylindolyl) | 2-thienyl |
| | | | **15a** | Ph | 3-(1-acetylindolyl) |
| | | | **b** | 2-thienyl | 2-furyl |
| | | | **c** | 3-(1-acetylindolyl) | 3-(1-acetylindolyl) |

**SCHEME 3** Reagents and conditions: (i) $ArCH{=}NNH_2$ (**13a–d**), EtOH, reflux; (ii) ArCHO, EtOH, reflux; (iii) $Ac_2O$, pyridene, r.t.; (iv) $Ac_2O$, reflux.

for the exocyclic double bond, in agreement with the $^1H$ NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoin derivatives whose vinyl protons respectively appear at $\delta$ 6.10–6.35 and $\delta$ 6.40–6.75.[15–17] On the other hand, when compounds **1c**, **2b** and **3c** were treated with refluxing acetic anhydride the corresponding 5-[(*Z*)-arylidene]-3-acetyl-2-(1-acetyl-2-(*E*)-arylidenehydrazono)-4-imidazolidinones **15a–c** were produced. The structures of **15a–c** were established on the basis of their elemental analyses and spectral data (IR, $^1H$ NMR, $^{13}C$ NMR and MS). The structure of **15a** was supported by its mass spectra, which showed a molecular ion peak at *m/z* 455 and its $^1H$ NMR ($CDCl_3$) spectrum showed the anomeric proton as a singlet at $\delta$ 7.78, indicating the presence of only the *Z*-configuration of the exocyclic double bond. This is

confirmed by its $^{13}C$ NMR NMR ($CDCl_3$) spectrum which shows a singlet at 114.54 ppm assigned to the vinylic carbon. The corresponding carbon [$CDCl_3$] for 5-(*Z*)- and 5-(*E*)-arylidenehydantoin derivatives give signals at 105–115 ppm and 115–125 ppm[15–17] respectively (Scheme 3).

The synthesis of compounds **5–7** was then carried out. Thus, 2-(*E*)-monosaccharides hydrazones **16a–c** were prepared according to the published methods[1] via the condensation of hydrazine hydrate and monosaccharides including *D*-galactose, *D*-mannose and *L*-arabinose in anhydrous methanol at room temperature. Compounds **16a–c** were condensed with 5-[(*Z*)-arylidene]-2-mercaptohydantoins **8a–c** in refluxing methanol to afford the corresponding 5-[(*Z*)-arylidene]-2-((2-(*E*)-polyhydroxyalkylidene)hydrazono)-4-imidazolidinones **5a–c** to **7a–c**. The structures of **5a–c** to **7a–c** were established on the basis of their elemental analyses and spectral data (IR, $^1H$ NMR, $^{13}C$ NMR, and MS). Analytical data for compound **5a** revealed a molecular formula $C_{14}H_{18}N_4O_6S$ (*m/z* 370). The $^1H$ NMR spectrum of compound **5a** showed the presence of a singlet at $\delta$ 6.73 assigned to the vinylic proton, proving a *Z*-configuration of the exocyclic double bond. The doublet at $\delta$ 7.46 with $J = 7.52$ Hz was due to H-1′, and the doublet at $\delta$ 4.52 with $J = 6.97$ Hz were assigned to H-2′, indicating the presence of *E*-configuration of the other exocyclic double bond, in accordance with the reported results for *D*-ribose *E*-hydrazone and *D*-ribose *Z*-hydrazone which showed signals for H-1, H-2 at $\delta$ 6.70–7.40, 4.10–4.70 and $\delta$ 6.50–6.80, 4.80–5.30 respectively.[19] Compound **5a** was also independently synthesized through another pathway via condensation of **9a** with *D*-galactose in refluxing methanol for 24 h (47%). Treatment of compounds **5b**,**c** and/or **6a–c** with acetic anhydride in pyridine at room temperature gave the corresponding 5-[(*E*)-2-arylidene]-2-(1-acetyl-2-(*E*)-(polyacetylalkylidenehydrazono)-4-imidazolidinones **17a–e**. On the other hand, treatment of compounds **5b** with benzoyl chloride in pyridine at room temperature gave the corresponding 5-[(*Z*)-2-arylidene]-2-(1-benzoyl-2-(*E*)-(2,3,4,5,6-penta-*O*-benzoylhexylidenehydrazono)-4-imidazolidinone (**18**). The structures of **17a–e** and **18** were established on the basis of their elemental analyses and spectral data (IR, $^1H$ NMR, $^{13}C$ NMR and MS). Analytical data for compound **17b** revealed a molecular formula $C_{32}H_{36}N_5O_{13}$ (*m/z* 697). The IR spectrum of compound **17b** was characterized by the absence of an hydroxy groups of the galactose moiety and the presence of an acetoxy carbonyl at 1754 $cm^{-1}$. The $^1H$ NMR spectrum of compound **17b** showed a singlet at $\delta$ 6.70 assigned to a vinylic proton. This proves a *Z*-configuration of the exocyclic double bond. The doublet at $\delta$ 6.62 with a spin-spin coupling constant equal to 9.52 Hz, corresponding to the orientation of H-1′ and H-2′ protons.

**TABLE I** IR and $^1$H NMR Data for **1–18**

| Compound | IR (KBr) ($cm^{-1}$) | $^1$H NMR ($D_3C)_2SO/\delta$ |
|---|---|---|
| **1a** | 3142 (NH), 1728 (CO) | 11.57 (s, 1H, NH), 10.65 (br. s, 1H, NH), 8.20 (s, 1H, HC═N), 7.90–7.12 (m, 8 H, Ar─H), 6.75 (s, 1H, HC═C) |
| **1b** | 3144 (NH), 1730 (CO) | 11.86 (s, 1H, NH), 10.81 (s, 1H, NH), 8.32 (s, 1H, HC═N), 7.95–6.62 (m, 8 H, Ar─H), 6.30 (s, 1H, HC═C) |
| **1c** | 3141 (NH), 1729 (CO) | 11.71 (s, 1H, NH), 11.62 (s, 1H, NH), 10.57 (br. s, 1H, NH), 8.26 (s, 1H, HC═N), 8.21–7.10 (m, 10 H, Ar─H), 6.73 (s, 1H, HC═C) |
| **2a** | 3147 (NH), 1728 (CO) | 11.75 (s, 1H, NH), 10.55 (br. s, 1H, NH), 8.23 (s, 1H, HC═N), 7.80–7.15 (m, 6 H, Ar─H), 6.72 (s, 1H, HC═C) |
| **2b** | 3145 (NH), 1726 (CO) | 11.74 (s, 1H, NH), 10.53 (br. s, 1H, NH), 8.58 (s, 1H, HC═N), 8.50–6.62 (m, 6 H, Ar─H), 6.27 (s, 1H, HC═C) |
| **2c** | 3146 (NH), 1724 (CO) | 11.85 (s, 1H, NH), 11.76 (s, 1H, NH), 10.46 (br. s, 1H, NH), 8.32 (s, 1H, HC═N), 8.40–7.13 (m, 8 H, Ar─H), 6.70 (s, 1H, HC═C) |
| **3a** | 3146 (NH), 1733 (CO) | 11.78 (s, 1H, NH), 11.67 (s, 1H, NH), 10.50 (br. s, 1H, NH), 8.85 (s, 1H, HC═N), 8.39–7.08 (m, 8 H, Ar─H), 6.70 (s, 1H, HC═C) |
| **3b** | 3142 (NH), 1726 (CO) | 11.73 (s, 1H, NH), 11.52 (s, 1H, NH), 10.48 (br. s, 1H, NH), 8.90 (s, 1H, HC═N), 8.40–6.65 (m, 8 H, Ar─H), 6.28 (s, 1H, HC═C) |
| **3c** | 3140 (NH), 1727 (CO) | 11.68 (s, 2 H, 2 NH), 11.51 (s, 2 H, $N_1$-H, NH), 8.98 (s, 1H, HC═N), 8.37–7.08 (m, 8 H, Ar─H), 6.66 (s, 1H, HC═C) |
| **4a** | 3143 (NH), 1732 (CO) | 11.73 (s, 1H, NH), 10.65 (br. s, 1H, NH), 8.26 (s, 1H, HC═N), 8.10–6.72 (m, 6 H, Ar─H), 6.70 (s, 1H, HC═C) |
| **4b** | 3146 (NH), 1728 (CO) | 11.70 (s, 1H, NH), 10.60 (br. s, 1H, NH), 8.17 (s, 1H, HC═N), 8.00–6.63 (m, 6 H, Ar─H), 6.25 (s, 1H, HC═C) |
| **5a** | 3436 (OH), 3192 (NH), 1718 (CO) | 11.51 (s, 1H, NH), 10.45 (br. s, 1H, NH), 7.61 (d, 1H, H-3), 7.55 (d, 1H, H-5), 7.46 (d, $J_{1'-2'} = 7.52$ Hz, 1H, H-1′), 7.09 (t, 1H, H-4), 6.73 (s, 1H, HC═C), 4.90 (d, 1H, 2′-OH), 4.52 (m, 3 H, H-2′, H-3′, 3′-OH), 4.18 (m, 2 H, 5′-OH, 4′-OH), 3.68 (t, 1H, 6′-OH), 3.55 (m, 2 H, H-5′, H-4′), 3.45–3.28 (m, 2 H, H-6′, H-6″) |
| **5b** | 3438 (OH), 3190 (NH), 1720 (CO) | 11.60 (s, 1H, NH), 10.70 (br. s, 1H, NH), 7.70 (d, 1H, H-5), 7.66 (d, 1H, H-3), 6.92 (d, $J_{1'-2'} = 7.55$ Hz, 1H, H-1′), 6.59 (dd, 1H, H-4), 6.20 (s, 1H, HC═C), 4.65 (d, 1H, 2′-OH), 4.47 (m, 3 H, H-2′, H-3′, 3′-OH), 4.15 (m, 2 H, 5′-OH, 4′-OH), 3.70 (t, 1H, 6′-OH),″), 3.56 (m, 2 H, H-5′, H-4′), 3.47–3.27 (m, 2 H, H-6′, H-6″) |

**TABLE I** IR and $^1$H NMR Data for **1–18** *(Continued)*

| Compound | IR (KBr) ($cm^{-1}$) | $^1$H NMR $(D_3C)_2SO/\delta$ |
|---|---|---|
| **5c** | 3436 (OH), 3200 (NH), 1724 (CO) | 11.56 (s, 1H, NH), 10.50 (br. s, 1H, NH), 8.37 (d, 1H, H-2), 8.14 (d, 1H, H-7), 7.46 (d, $J_{1'-2'} = 7.68$ Hz, 1H, H-1′), 7.11–7.23 (m, 3 H, H-4, H-5, H-6), 6.70 (s, 1H, HC═C), 4.70 (d, 1H, 2′-OH), 4.50 (m, 3 H, H-2′, H-3′, 3′-OH), 4.20 (m, 2 H, 5′-OH, 4′-OH), 3.76 (t, 1H, 6′-OH), 3.60 (m, 2 H, H-5′, H-4′), 3.50–3.30 (m, 2 H, H-6′, H-6″) |
| **6a** | 3435 (OH), 3196 (NH), 1725 (CO) | 11.72 (s, 1H, NH), 10.60 (br. s, 1H, NH), 7.62 (d, 1H, H-3), 7.54 (d, 1H, H-5), 7.48 (d, $J_{1'-2'} = 6.38$ Hz, 1H, H-1′), 7.11 (t, 1H, H-4), 6.70 (s, 1H, HC═C), 4.92 (d, 1H, 2′-OH), 4.45 (m, 3 H, H-2′, H-3′, 3′-OH), 4.20 (m, 2 H, 5′-OH, 4′-OH), 3.65 (t, 1H, 6′-OH), 3.52–3.30 (m, 4 H, H-6′, H-6″, H-5′, H-4′) |
| **6b** | 3433 (OH), 3202 (NH), 1723 (CO) | 11.70 (s, 1H, NH), 10.65 (br. s, 1H, NH), 7.72 (d, 1H, H-5), 7.68 (d, 1H, H-3), 7.08 (d, $J_{1'-2'} = 6.35$ Hz, 1H, H-1′), 6.60 (dd, 1H, H-4), 6.25 (s, 1H, HC═C), 4.68 (d, 1H, 2′-OH), 4.50 (m, 3 H, H-2′, H-3′, 3′-OH), 4.20 (m, 2 H, 5′-OH, 4′-OH), 3.75 (t, 1H, 6′-OH), ″), 3.56 (m, 2 H, H-5′, H-4′), 3.46–3.25 (m, 2 H, H-6′, H-6″) |
| **6c** | 3430 (OH), 3197 (NH), 1718 (CO) | 11.72 (s, 1H, NH), 11.56 (s, 1H, $N_3$-H), 10.50 (br. s, 1H, $N_1$-H), 8.38 (d, 1H, H-2), 8.18 (d, 1H, H-7), 7.80 (d, $J_{1'-2'} = 6.25$ Hz, 1H, H-1′), 7.45 (t, 1H, H-6), 7.15 (m, 2 H, H-4, H-5), 6.70 (s, 1H, HC═C), 4.92 (d, 1H, 2′-OH), 4.42 (m, 3 H, H-2′, H-3′, 3′-OH), 4.18 (m, 2 H, 5′-OH, 4′-OH), 3.60 (t, 1H, 6′-OH), 3.56–3.30 (m, 4 H, H-6′, H-6″, H-5′, H-4′) |
| **7a** | 3430 (OH), 3192 (NH), 1722 (CO) | 11.51 (s, 1H, NH), 10.45 (br. s, 1H, NH), 7.61 (d, 1H, H-3), 7.55 (d, 1H, H-5), 7.46 (d, $J_{1'-2'} = 6.56$ Hz, 1H, H-1′), 7.08 (t, 1H, H-4), 6.70 (s, 1H, HC═C), 4.82 (d, 1H, 2′-OH), 4.61 (m, 2 H, 3′-OH, 4′-OH), 4.42 (m, 2 H, H-2′, H-3′), ), 3.80 (t, 1H, 5′-OH), 3.65–3.20 (m, 4 H, H-5′, H-5″, H-4′) |
| **7b** | 3435 (OH), 3210 (NH), 1728 (CO) | 11.30 (s, 1H, NH), 10.80 (br. s, 1H, NH), 7.71 (d, 1H, H-5), 7.66 (d, 1H, H-3), 6.92 (d, $J_{1'-2'} = 6.34$ Hz, 1H, H-1′), 6.61 (d, 1H, H-4 furyl), 6.22 (s, 1H, HC═C), 4.78 (d, 1H, 2′-OH), 4.67 (m, 2 H, 3′-OH, 4′-OH), 4.50 (m, 2 H, H-2′, H-3′), 3.72 (t, 1H, 5′-OH), 3.60–3.20 (m, 3 H, H-5′, H-5″, H-4′) |

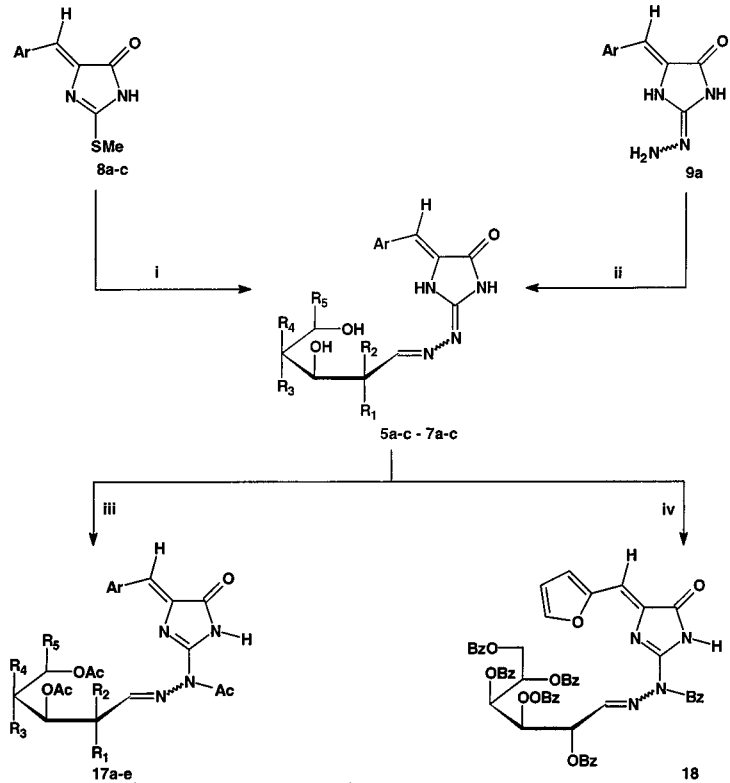
*(Continued on next page)*

**TABLE I** IR and $^1$H NMR Data for **1–18** *(Continued)*

| Compound | IR (KBr) ($cm^{-1}$) | $^1$H NMR ($D_3C)_2SO/\delta$ |
|---|---|---|
| **7c** | 3433 (OH), 3196 (NH), 1720 (CO) | 11.75 (s, 1H, NH), 11.62 (s, 1H, NH), 10.56 (br. s, 1H, NH), 8.40 (d, 1H, H-2), 8.20 (d, 1H, H-7), 7.75 (d, $J_{1'-2'} = 6.30$ Hz, 1H, H-1′), 7.50 (t, 1H, H-6), 7.20 (m, 2 H, H-4, H-5), 6.72 (s, 1H, HC═C), 4.85 (d, 1H, 2′-OH), 4.60 (m, 2 H, 3′-OH, 4′-OH), 4.35 (m, 2 H, H-2′, H-3′), 3.75 (t, 1H, 5′-OH), 3.60–3.30 (m, 3 H, H-5′, H-5″, H-4′) |
| **8a** | 3192 (NH), 1718 (CO) | 11.80 (s, 1H, NH), 7.86 (d, 1H, H-3), 7.68 (d, 1H, H-5), 7.22 (s, 1H, ═CH), 7.18 (dd, 1H, H-4), 2.64 (s, 3 H, SMe) |
| **8b** | 3198 (NH), 1719 (CO) | 11.78 (s, 1H, NH), 7.88 (d, 1H, H-5), 7.36 (d, 1H, H-3), 6.71 (dd, 1H, H-4), 6.32 (s, 1H, ═CH), 2.66 (s, 3 H, SMe) |
| **8c** | 3194 (NH), 1720 (CO) | 12.02 (d, 1H, NH), 11.56 (s, 1H, NH), 7.15–8.60 (m, 6 H, ═CH, Ar—H), 2.63 (s, 3 H, SMe) |
| **9a** | 3312 ($NH_2$), 3157 (NH), 1722 (CO) | 11.80 (br. s, 2 H, 2NH), 7.90 (d, 1H, H-3), 7.82 (d, 1H, H-5), 7.20 (t, 1H, H-4), 6.74 (s, 1H, ═CH), 5.20 (br. s, 2 H, $NH_2$) |
| **9b** | 3320 ($NH_2$), 3152 (NH), 1719 (CO) | 11.78 (br. s, 1H, 2NH), 7.86 (d, 1H, H-5), 7.21 (d, 1H, H-3), 6.70 (dd, 1H, H-4), 6.35 (s, 1H, ═CH), 5.18 (br. s, 2 H, $NH_2$) |
| **9c** | 3314 ($NH_2$), 3149 (NH), 1725 (CO) | 11.56 (br. s, 3 H, 3NH), 8.17–7.06 (m, 5 H, Ar—H), 6.64 (s, 1H, ═CH), 5.10 (br. s, 2 H, $NH_2$) |
| **12a** | 3143 (NH), 1727 (CO) | 11.82 (br. s, 2 H, 2NH), 7.90 (d, 1H, H-3), 7.64 (d, 1H, H-5), 7.12 (t, 1H, H-4), 6.75 (s, 1H, ═CH) |
| **12b** | 3145 (NH), 1725 (CO) | 11.67 (br. s, 2 H, 2NH), 7.70 (d, 1H, H-5), 7.60 (d, 1H, H-3), 6.60 (dd, 1H, H-4), 6.30 (s, 1H, ═CH) |
| **12c** | 3148 (NH), 1728 (CO) | 12.02 (d, J = 2.30 Hz, 1H, 1NH), 11.50 (br. s, 2 H, 2NH), 8.14–7.11 (m, 5 H, Ar—H), 6.70 (s, 1H, ═CH) |
| **14a** | 3204 (NH), 1752 (Ac), 1727 (CO) | 11.70 (s, 1H, NH), 8.25 (s, 1H, HC═N), 7.60–7.10 (m, 8 H, Ar—H), 6.82 (s, 1H, HC═C), 2.60 (s, 3 H, Ac) |
| **14b** | 3200 (NH), 1755 (Ac), 1730 (CO) | 11.68 (s, 1H, NH), 8.45 (s, 1H, HC═N), 8.35–6.68 (m, 8 H, Ar—H), 6.35 (s, 1H, HC═C), 2.58 (s, 3 H, Ac) |
| **14c** | 3211 (NH), 1757 (Ac), 1728 (CO) | 11.68 (s, 1H, $N_3$—H), 8.86 (s, 1H, HC═N), 8.40–7.15 (m, 10 H, Ar—H), 6.70 (s, 1H, HC═C), 2.98, 2.58 (2s, 6 H, s, 2 Ac) |
| **14d** | 3208 (NH), 1758 (Ac), 1725 (CO) | 11.75 (s, 1H, NH), 8.78 (s, 1H, HC═N), 8.42–7.12 (m, 10 H, Ar—H), 6.75 (s, 1H, HC═C), 3.15, 2.56 (2s, 6 H, s, 2 Ac) |
| **15a** | 1752 (Ac), 1727 (CO) | 8.57 (s, 1H, HC═N), 8.48–7.41 (m, 11H, Ar—H, HC═C), 2.68, 2.64, 2.54 (3s, 9 H, 2 Ac) |

**TABLE I** IR and $^1$H NMR Data for **1–18** *(Continued)*

| Compound | IR (KBr) ($cm^{-1}$) | $^1$H NMR $(D_3C)_2SO/\delta$ |
|---|---|---|
| **15b** | 1750 (Ac), 1728 (CO) | 8.45 (s, 1H, HC═N), 8.10–6.70 (m, 6 H, Ar—H), 6.38 (s, 1H, HC═C), 2.82, 2.56 (2s, 6 H, 2 Ac) |
| **15c** | 1756 (Ac), 1729 (CO) | 8.85 (s, 1H, HC═N), 8.38–7.10 (m, 10 H, Ar—H), 6.72 (s, 1H, HC═C), 3.08, 3.18, 2.78, 2.58 (2s, 12 H, 4 Ac) |
| **17a** | 3196 (NH), 1758 (Ac), 1717 (CO) | 11.76 (s, 1H, NH), 7.76 (d, 1H, H-5), 7.68 (d, 1H, H-3), 6.60 (dd, 1H, H-4), 6.55 (d, $J_{1'-2'} = 9.50$ Hz, 1H, H-1′), 6.25 (s, 1H, HC═C), 5.56 (dd, 1H, H-2′), 5.42 (m, 1H, H-3′), 5.40 (m, 1H, H-4′), 5.30 (m, 1H, H-5′), 4.22 (dd, 1H, H-6″), 3.85 (dd, 1H, H-6′), 2.50, 2.12, 2.06, 2.00 (4 s, 18 H, 5 Ac) |
| **17b** | 3202 (NH), 1754 (Ac), 1719 (CO) | 11.74 (s, 1H, NH), 8.34 (s, 1H, H-2), 8.15 (d, 1H, H-7), 7.25 (d, 1H, H-6), 7.12 (m, 2 H, H-4, H-5), 6.70 (s, 1H, HC═C), 6.62 (d, $J_{1'-2'} = 9.52$ Hz, 1, H, H-1′), 5.60 (dd, 1H, H-2′), 5.45 (m, 1H, H-3′), 5.40 (m, 1H, H-4′), 5.32 (m, 1H, H-5′), 4.25 (dd, 1H, H-6″), 3.78 (dd, 1H, H-6′), 3.05, 2.58, 2.08, 2.02, 1.98 (5s, 15 H, 5 Ac) |
| **17c** | 3192 (NH), 1755 (Ac), 1720 (CO) | 11.56 (s, 1H, $N_3$—H), 7.60 (d, 1H, H-3), 7.50 (d, 1H, H-5), 7.08 (t, 1H, H-4), 6.75 (s, 1H, HC═C), 6.60 (d, $J_{1'-2'} = 9.25$ Hz, 1H, H-1′), 5.75 (t, 1H, H-2′), 5.48 (m, 1H, H-3′), 5.22 (m, 1H, H-4′), 4.30 (dd, 1H, H-5″), 4.15 (dd, 1H, H-5′), 2.54, 2.13, 2.10, 2.06, 2.03 (5s, 15 H, 5 Ac) |
| **17d** | 3194 (NH), 1757 (Ac), 1728 (CO) | 11.75 (s, 1H, $N_3$—H), 7.80 (d, 1H, H-5), 7.68 (d, 1H, H-3), 6.61 (dd, 1H, H-4), 6.52 (d, $J_{1'-2'} = 9.20$ Hz, 1H, H-1′), 6.30 (s, 1H, HC═C), 5.76 (dd, 1H, H-2′), 5.50 (m, 1H, H-3′), 5.25 (m, 1H, H-4′), 4.32 (m, 1H, H-5″), 4.16 (dd, 1H, H-5′), 2.60, 2.11, 2.08, 2.02, 2.00 (5s, 15 H, 5 Ac) |
| **17e** | 3204 (NH), 1750 (Ac), 1718 (CO) | 11.70 (s, 1H, $N_3$—H), 8.35 (s, 1H, H-2), 8.20 (d, 1H, H-7), 7.25 (d, 1H, H-6), 7.15 (m, 2 H, H-4, H-5), 6.74 (s, 1H, HC═C), 6.60 (d, $J_{1'-2'} = 9.26$ Hz, 1H, H-1′), 5.70 (dd, 1H, H-2′), 5.50 (dd, 1H, H-3′), 5.24 (m, 1H, H-4′), 4.30 (dd, 1H, H-5″), 4.12 (dd, 1H, H-5′), 3.12, 2.60, 2.12, 2.08, 2.03, 1.98 (5 s, 15 H, 5 Ac) |
| **18** | 3204 (NH), 1750 (Ac), 1718 (CO) | 11.56 (s, 1H, NH), ), 8.50–6.60 (m, 33 H, Ar—H), 6.59 (d, $J_{1'-2'} = 9.55$ Hz, 1H, H-1′), 6.35 (s, 1H, HC═C), 5.60 (dd, 1H, H-2′), 5.54 (m, 1H, H-3′), 5.48 (m, 1H, H-4′), 5.40 (m, 1H, H-5′), 4.30 (dd, 1H, H-6″), 4.08 (dd, 1H, H-6′) |




| | Ar | | | |
|---|---|---|---|---|
| **5a-c** = *D*-galacto | **a:** 2-thienyl | **17a** | *D*-galactopentaacetate | **a:** Ar = 2-furyl |
| **6a-c** = *D*-manno | **b:** 2-furyl | **b** | *D*-galactopentaacetate | **b:** Ar = 3-(1-acetylindolyl) |
| **7a-c** = *L*-arabino | **c:** 3-indolyl | **c** | *L*-arabinotetraacetate | **c:** Ar = 2-thienyl |
| | | **d** | *L*-arabinotetraacetate | **d:** Ar = 2-furyl |
| | | **e** | *L*-arabinotetraacetate | **e:** Ar = 3-(1-acetylindolyl) |

**SCHEME 4** Reagents and conditions: (i) 2-(*E*)-monosaccarides hydrazones (**16a–c**), MeOH, reflux; (ii) monosaccarides, $NH_2NH_2{\cdot}H_2O$, MeOH, reflux; (iii) $Ac_2O$, pyridene, r.t.; (iv) $H_5C_6COCl$, pyridene, r.t.

This indicates the presence of the *E*-configuration of the other exocyclic double bond (Scheme 4).

## Biological Evaluation

Compounds **1a–c** to **7a–c** were tested against HIV-1 (HTLV IIIB) in MT-4 cells and were found to be inactive.[20] For antitumor activities, the compounds **1a–c** to **7a–c** were screened against leukaemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer,

**TABLE II** $^{13}C$ NMR Data for Some Selected Compounds Listed in Table I

| Compound | $^{13}C$ NMR $(D_3C)_2SO/\delta$ |
|---|---|
| **1a** | 168.70 (C-1′), 161.75 (C-4), 157.00 (C-2), 127.67, 127.99, 128.80, 129.16, 129.31, 129.33, 129.97, 129.99, 130.02, 134.04, 138.28 (C—Ar, C-5), 106.09 (=HC) |
| **1b** | 169.68 (C-1′), 163.16 (C-4), 152.44 (C-2), 93.86, 111.01, 123.82, 126.00, 126.95, 128.02, 142.12, 148.25, 150.54 (C—Ar, C-5), 110.09 (=CH) |
| **10b** | 169.96 (C-2), 164.27 (C-4), 150.50 (C-2), 145.33 (C-5), 136.94 (C-5), 116.51 (C-3), 113.26 (=CH), 108.24 (C-4), 12.12 (Me) |

renal cancer, prostate cancer, and breast cancer and were found to be inactive.[21,22]

## EXPERIMENTAL

NMR spectra were measured on a Bruker Advance DPX 300 MHz spectrometers for solutions in DMSO-$d_6$ using TMS as internal standard. The chemical shifts are given as $\delta$ values, and the $J$ values are given in Hz. Mass spectra were recorded on a Varian MAT 112 spectrometer. Melting points (°C, uncorrected) were recorded on a Gallenkamp melting point apparatus. Aluminium sheets coated with silica gel 60 $F_{254}$ (Merck) were used for TLC. Detection was effected by viewing under a short wavelength UV lamp. IR spectra (KBr disc) were obtained on a Pye Unicam Spectra 1000. Analytical data were performed on C, H, N, Elemental analyzer Carls Erba 1106.

*5-(Z)-Arylidene-2-thiohydantoins* (**11a–c**). To a mixture of 2-thiohydantoin (10, 1.16 g, 10 mmol), piperidine (3 drops), and absolute ethanol (30 ml) was added the appropriate aromatic aldehydes (10 mmol). The reaction mixture was stirred 12 h at room temperature until the starting material was consumed (TLC). The reaction mixture was diluted with cold water, followed by neutralization with diluted hydrochloric acid. The separated yellow solid was collected by filtration and recrystallized from ethanol to give the products **11a–c**.[7]

*5-[Z)-Arylidene]2-methylmercaptohydantoins* (**8a–c**). Compounds **11a–c** (10 mmol) were suspended in aq. sodium hydroxide (12.60 %, 3.50 ml) at room temperature To this suspension was added 25 ml of methanol, and the mixture become clear after stirring 5 min. Methyl iodide (1.56 g, 11 mmol) was added, and the mixture was stirred 12 h at room temperature. The separated yellow solid was collected by filtration and recrystallized from methanol to afford the products **8a–c**.

**TABLE III** Melting Points, Yields, and Analytical Data for **1–18**

| Compound | Melting point (°C) | Yield (g, %) | Molecular formula (MW) | Found/Calculated (%) C | H | N | $M^+$ ($m/z$) |
|---|---|---|---|---|---|---|---|
| **1a** | 238 | 2.3, 78 | $C_{15}H_{12}N_4OS$ (296) | 60.6/60.8 | 4.4/4.1 | 19.0/18.9 | 296 |
| **1b** | 270 | 1.82, 68 | $C_{15}H_{12}N_4O_2$ (280) | 64.4/64.3 | 4.6/4.3 | 19.7/20.0 | 280 |
| **1c** | 294 | 2.00, 61 | $C_{19}H_{15}N_5O$ (329) | 69.0/69.3 | 4.8/4.6 | 21.1/21.3 | 329 |
| **2a** | 245 | 2.11, 70 | $C_{13}H_{10}N_4OS_2$ (302) | 51.3/51.6 | 3.5/3.3 | 18.4/18.5 | 302 |
| **2b** | 252 | 1.52, 53 | $C_{13}H_{10}N_4O_2S$ (286) | 54.2/54.5 | 3.8/3.5 | 19.7/19.6 | 286 |
| **2c** | 297 | 2.01, 60 | $C_{17}H_{13}N_5OS$ (335) | 60.5/60.9 | 4.2/3.9 | 20.7/20.9 | 335 |
| **3a** | 350 | 2.91, 87 | $C_{17}H_{13}N_5OS$ (335) | 60.7/60.9 | 4.1/3.9 | 20.6/20.9 | 335 |
| **3b** | 249 | 2.52, 79 | $C_{17}H_{13}N_5O_2$ (319) | 63.7/63.9 | 4.4/4.1 | 21.5/21.9 | 319 |
| **3c** | 287 | 3.42, 93 | $C_{21}H_{16}N_6O$ (368) | 68.2/68.5 | 4.5/4.4 | 22.6/22.8 | 368 |
| **4a** | 205 | 1.97, 69 | $C_{13}H_{10}N_4O_2S$ (286) | 54.4/54.5 | 3.8/3.5 | 19.3/19.6 | 286 |
| **4b** | 210 | 1.94, 72 | $C_{13}H_{10}N_4O_3$ (270) | 57.7/57.8 | 3.9/3.7 | 20.4/20.7 | 270 |
| **5a** | 215 | 2.81, 76 | $C_{14}H_{18}N_4O_6S$ (370) | 45.1/45.4 | 5.2/4.9 | 14.8/15.1 | 370 |
| **5b** | 220 | 2.55, 72 | $C_{14}H_{18}N_4O_7$ (354) | 47.3/47.5 | 5.2/5.1 | 15.5/15.8 | 354 |
| **5c** | 240 | 3.06, 76 | $C_{18}H_{21}N_5O_6$ (403) | 53.3/53.6 | 5.3/5.2 | 17.6/17.4 | 403 |
| **6a** | 192 | 2.59, 70 | $C_{14}H_{18}N_4O_6S$ (370) | 45.2/45.4 | 5.1/4.9 | 14.9/15.1 | 370 |
| **6b** | 180 | 2.58, 73 | $C_{14}H_{18}N_4O_7$ (354) | 47.2/47.5 | 5.4/5.1 | 15.5/15.8 | 354 |
| **6c** | 198 | 2.74, 68 | $C_{18}H_{21}N_5O_6$ (403) | 53.5/53.6 | 5.5/5.2 | 17.1/17.4 | 403 |
| **7a** | 190 | 2.79, 82 | $C_{13}H_{16}N_4O_5S$ (340) | 45.7/45.9 | 5.0/4.7 | 16.4/16.5 | 340 |
| **7b** | 198 | 1.68, 52 | $C_{13}H_{16}N_4O_6$ (324) | 47.8/48.1 | 5.4/5.0 | 17.1/17.3 | 324 |
| **7c** | 177 | 2.98, 80 | $C_{17}H_{19}N_5O_5$ (373) | 54.6/54.5 | 5.5/5.2 | 18.7/18.5 | 373 |
| **8a** | 214 | 2.06, 92 | $C_9H_8N_2OS_2$ (224) | 47.9/48.2 | 3.4/3.6 | 12.3/12.5 | 224 |
| **8b** | 168 | 1.81, 87 | $C_9H_8N_2O_2S$ (208) | 51.6/51.9 | 3.7/3.9 | 13.3/13.5 | 208 |
| **8c** | 242 | 2.48, 96 | $C_{13}H_{11}N_3OS$ (257) | 60.5/60.7 | 4.4/4.3 | 15.9/16.3 | 257 |
| **9a** | 276 | 0.58, 28 | $C_8H_8N_4OS$ (208) | 45.9/46.1 | 3.8/3.9 | 26.5/26.9 | 208 |
| **9b** | 212 | 0.48, 25 | $C_8H_8N_4O_2$ (192) | 49.6/50.0 | 3.9/4.2 | 28.9/29.2 | 192 |
| **9c** | 273 | 1.15, 48 | $C_{12}H_{11}N_5O$ (241) | 59.5/59.7 | 4.9/4.6 | 28.6/29.0 | 241 |
| **12a** | 312 | 2.72, 96 | $C_{16}H_{12}N_6O_2S_2$ (284) | 49.8/50.0 | 3.4/3.1 | 21.7/21.9 | 284 |
| **12b** | 298 | 2.88, 82 | $C_{16}H_{12}N_6O_4$ (352) | 54.4/54.5 | 3.7/3.4 | 23.6/23.9 | 352 |
| **12c** | 318 | 4.05, 90 | $C_{24}H_{18}N_8O_2$ (450) | 63.7/64.0 | 4.2/4.0 | 24.8/24.9 | 450 |
| **14a** | 202 | 2.97, 88 | $C_{17}H_{14}N_4O_2S$ (338) | 60.0/60.3 | 4.4/4.2 | 16.5/16.6 | 338 |
| **14b** | 190 | 2.64, 88 | $C_{17}H_{14}N_4O_3$ (322) | 63.2/63.3 | 4.7/4.4 | 17.2/17.4 | 322 |
| **14c** | 217 | 3.76, 91 | $C_{23}H_{19}N_5O_3$ (413) | 66.4/66.8 | 4.9/4.6 | 16.6/16.9 | 413 |
| **14d** | 244 | 3.56, 85 | $C_{21}H_{17}N_5O_3S$ (419) | 59.9/60.1 | 4.5/4.1 | 16.5/16.7 | 419 |
| **15a** | 224 | 3.96, 87 | $C_{25}H_{21}N_5O_4$ (455) | 65.7/65.9 | 4.9/4.6 | 15.3/15.4 | 455 |
| **15b** | 160 | 3.03, 82 | $C_{17}H_{14}N_4O_4S$ (370) | 55.0/55.1 | 4.0/3.8 | 14.8/15.1 | 370 |
| **15c** | 230 | 4.66, 87 | $C_{29}H_{24}N_6O_5$ (536) | 64.8/64.9 | 4.8/4.5 | 15.3/15.7 | 536 |
| **17a** | 197 | 4.60, 76 | $C_{26}H_{30}N_4O_{13}$ (606) | 51.1/51.5 | 5.3/5.0 | 8.8/9.2 | 606 |
| **17b** | 222 | 5.26, 77 | $C_{32}H_{36}N_5O_{13}$ (697) | 54.8/55.1 | 5.4/5.1 | 9.7/10.0 | 697 |
| **17c** | 170 | 4.62, 84 | $C_{23}H_{26}N_4O_{10}S$ (550) | 49.8/50.2 | 5.1/4.8 | 10.0/10.2 | 550 |
| **17d** | 168 | 3.20, 60 | $C_{23}H_{26}N_4O_{11}$ (534) | 51.4/51.7 | 5.3/4.9 | 10.3/10.5 | 534 |
| **17e** | 156 | 5.25, 84 | $C_{29}H_{31}N_5O_{11}$ (625) | 55.3/55.7 | 5.1/5.0 | 11.0/11.2 | 625 |
| **18** | 155 | 8.02, 82 | $C_{56}H_{42}N_4O_{13}$ (978) | 68.3/68.7 | 4.0/4.3 | 5.6/5.7 | 978 |

## General Procedures for the Reaction of Hydrazine Hydrate with 8a–c

*Method A*. A suspension of **8a–c** (10 mmol) in absolute ethanol (20 ml) and hydrazine hydrate (2 ml) was heated under reflux for 12 h until the starting material was consumed (TLC), and the odor of methanethiol could not be detected. It was left to cool, and the separated yellow product was collected by filtration and recrystallized (ethanol) to afford 5-[(*Z*)-arylidene]-2-hydrazono-4-imidazolidinones (**9a–c**).

*Method B*. A mixture of each **8a–c** (10 mmol) and a slight excess of hydrazine hydrate (0.55 g, 11 mmol) in glacial acetic (2 ml) was refluxed for 4 h until the starting material was consumed (TLC), and the odor of methanethiol could not be detected. After cooling, the separated yellow solid was washed with ethanol and recrystallized (DMF) to yield *N*,*N*-bis-(5-(*Z*)-arylidene-4-oxo-2-imidazolidinylidene)hydrazines (**12a–c**).

## General Procedures for the Preparation of 5-[(*Z*)-Arylidene]-2-[(2-(*E*)-arylidene]hydrazono)-4-imidazolidinones 1a–c to 4a,b

*Method A*. A mixture of 5-[(*Z*)-arylidene]-2-methylmercaptohydantoins **8a–c** (10 mmol) and 2-(*E*)-arylidene hydrazone **13a–c** (10 mmol) in ethanol (30 ml) was heated under reflux for 48 h until the starting material was consumed (TLC) and the evolution of methanethiol ceased. After cooling, the separated yellow solid was collected by filtration and recrystallized (EtOH) to give the products **1a–c** to **4a**,**b**.

*Method B*. A mixture of 5-[(*Z*)-2-thienylidene]-2-hydrazono-4-imidazolidinone **9a** (1.04 g, 5 mmol) and benzaldehyde (5.03 g, 5 mmol) in absolute ethanol (25 ml) was heated under reflux for 24 h until the starting material was consumed (TLC). The separated yellow solid was collected and recrystallized (EtOH) to give 0.80 g (54 %) of 5-[(*Z*)-2-thienylidene]-2-((2-(*E*)-benzylidene)hydrazono)-4-imidazolidinone **1a**.

## General Procedures for the Reaction of Acetic Anhydride with 1–4

*Method A*. A cold solution of **1a–c** and **4a** (0.5 g) in anhydrous pyridine (5 ml) was treated with acetic anhydride (5 ml). The reaction mixture was kept overnight at room temperature with occasional stirring and then poured on to crushed ice. The separated yellow solid was collected by filtration and recrystallized (EtOH) to give the products 5-[(*Z*)-arylidene]-2-(1-acetyl-2-(*E*)-arylidene)hydrazono)-4-imidazolidinones **14a–d**.

*Method B*. A solution of **1c**, **2b** and **3c** (0.5 g) in acetic anhydride (4 ml) was heated under reflux on a boiling water bath for 2 h.

The reaction mixture was cooled and poured on to crushed ice. The separated yellow solid was collected by filtration and recrystallized (EtOH) to give the products 5-[(*Z*)-arylidene]-3-acetyl-2-(1-acetyl-2-(*E*)-arylidene)hydrazono)-4-imidzolidinones **15a–c**.

## General Procedures for the Preparation of 5-[(*Z*)-Arylidene]-2-((2-(*E*)-polyhydroxyalkylidene)-hydrazono)-4-imidazolidinones 5a–c to 7a–c

*Method A—General Procedure*. A mixture of **8a–c** (0.01 mmol) and monosaccharide *E*-hydrazones (**16a–c**) (0.01 mmol) in methyl alcohol (50 ml) was heated under reflux for 48 h until the starting material was consumed (TLC) and the evolution of methanethiol ceased. The yellow solid, which separated, was collected and recrystallized (DMF) to afford the products **5a–c** to **7a–c**.

*Method B*. A mixture of 5-((*Z*)-2-thienylidene)-2-hydrazono-4-imidazolidinone **9a** (1.04 g, 5 mmol) and *D*-galactose (0.90 g, 5 mmol) in methanol (25 ml) was heated under reflux for 24 h until the starting material was consumed (TLC). The yellow solid, which separated, was collected by filtration and recrystallized (DMF) to give 5-[(*Z*)-2-thienylidene]-2-[(2-(*E*)-*D*-galactose]hydrazono)-4-imidazolidinone **5a** in 47% yield.

*5-[(Z)-Arylidene]-2-(1-acetyl-2-(E)-2,3,4,5,6-penta-O-acetyl-D-galactose)hydrazono)-4-imidazolidinones* (**17a–e**). A cold solution of **5b**,**c** and **7a–c** (0.5 g) in anhydrous pyridine (5 ml) was treated with acetic anhydride (5 ml). The reaction mixture was kept overnight at room temperature with occasional stirring and then poured on to crushed ice. The separated yellow solid was collected by filtration and recrystallized (ethanol) to give the products **17a–e**.

*5-[(Z)-2-Furylidene]-2-(1-benzoyl-2-[(E)-2′,3′,4′,5′,6′-penta-O-benzoyl-D-galactose]hydrazono)-4-imidazolidinone* (**18**). A cold solution of **5b** (0.5 g) in anhydrous pyridine (5 ml) was treated with benzoyl chloride (1 ml). The mixture was kept for overnight at room temperature with occasional shaking. It was poured on to crushed ice and the product was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol to give the product **18**.

## REFERENCES

[1] A. I. Khodair and P. Bertrand, *Tetrahedron*, **54,** 4859 (1998).
[2] A. I. Khodair and E. E. Ibrahim, *Nucleosides and Nucleotides*, **15,** 1927 (1996).
[3] N. Mehta, C. A. Risiger, and F. E. Soroko, *J. Med. Chem.*, **24,** 465 (1981).

[4] F. L. Wessels, T. J. Schwan, and S. F. Pong, *J. Pharm. Sci.*, **69,** 1102 (1980).
[5] K. R. Bharucha, V. Pavilinis, D. Ajdukovic, and H. M. Shrenk, *Ger. Fat*. 2, 329, 745 (1974) *Chem. Abstr*., **80,** 95948d (1974).
[6] A. I. Khodair, H. I. El-Subagh, and A. A. El-Emam, *Boll Chim. Farmaceutico*, **136,** 561 (1997).
[7] A. A. El-Barbary, A. I. Khodair, E. B. Pedersen, and C. Nielsen, *J. Med. Chem.*, **37,** 73 (1994).
[8] A. M. Al-Obaid, H. I. El-Subagh, A. I. Khodair, and M. M. A. Elmazar, *Anti-Cancer Drugs*, **7,** 873 (1996).
[9] A. G. Caldwell, C. J. Harris, R. Stepney, and N. Wittaker, *J. Chem. Soc., Perkin Trans.*, **1,** 495 (1980).
[10] E. De Clercq and R. T. Walker, *Progress in Medicinal Chemistry* (Elsevier, New York, 1986), vol. 23, chap. 5.
[11] C. K. Chu and S. J. Cutter, *Heterocycl. Chem*., **23,** 289 (1986).
[12] M. Monsigny, A. C. Roche, P. Midoux, C. Kiedu, and R. Mayer, *Lectins and Glycoconjugates in Oncology: Structure, Fonction, Clinical Application* (Spriger-Verlag Heideberg, 1988).
[13] K. Miyajima, B. Yasuui, M. Motoyama, S. Ishikawa, and K. Yasumura, Eur. Pat. 531, 812 (1993), *Chem. Abstr.*, **119,** 117247c (1993).
[14] K. Yasumura, K. Miyajima, T. Nagahama, S. Ishikawa, Y. Tohyama, and K. Sugiyama, *PCT. Int.*, **19,** 335 (1994); *Chem. Abstr.*, **122,** 314548q (1995).
[15] S. F. Tan, K. P. Ang, and Y. F. Fong, *J. Chem. Soc., Perkin Trans.*, **2,** 1941 (1986).
[16] A. A. El-Barbary, A. I. Khodair, and E. B. Pedersen, *J. Org. Chem.*, **58,** 5994 (1993).
[17] A. A. El-Barbary, A. I. Khodair, E. B. Pedersen, and C. Nielsen, *Nucleosides and Nucleotides*, **13,** 707 (1994).
[18] G. Lock and K. Stach, *Ber. Dtsch. Chem. Ges.*, **76,** 1292 (1943).
[19] C. Chavis, C. De Gourcy, and J. L. Imbach, *Carbohydr. Res.*, **135,** 13 (1984).
[20] O. W. Weislow, R. Kiser, D. Fine, J. Bader, R. H. Skoemaker, and M. R. Boyd, *J. Natl. Cancer Inst.*, **81,** 577 (1989).
[21] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Poull, D. Vistica, C. Hose, J. Langly, P. Cronise, A. Viagro-Wolff, M. Gray-Goodrish, H. Compell, and M. Boyd, *J. Natl. Cancer Inst.*, **83,** 757 (1991).
[22] M. R. Boyd and K. D. Poull, *Drug Dev. Res.*, **34,** 91 (1995).