Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

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Published online: 27 Oct 2006.

To cite this article: A. I. Khodair , A. A. El-barbary , Y. A. Abbas & D. R. Imam (2001) SYNTHESIS, REACTIONS AND CONFORMATIONAL ANALYSIS OF 5-ARYLIDENE-2-THIOHYDANTOINS AS POTENTIAL ANTIVIRAL AGENTS, Phosphorus, Sulfur, and Silicon and the Related Elements, 170:1, 261-278, DOI: 10.1080/10426500108040603

To link to this article: http://dx.doi.org/10.1080/10426500108040603

Phosphorus, Sulfur and Silicon, 2001, Vol. 170, pp. 261-278
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SYNTHESIS, REACTIONS AND CONFORMATIONAL ANALYSIS OF 5-ARYLIDENE-2-THIOHYDANTOINS AS POTENTIAL ANTIVIRAL AGENTS

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(Received September 1, 2000; In final form November 29, 2000)

(*Z*)-5-Arylidene-1-(4-methylphenylsulfonyl)-2-thiohydantoins **5a,b** were synthesized from the direct condensation of the aromatic aldehydes **4a,b** with 1-(4-methylphenylsulfonyl)-2-thiohydantoins **3a,b**. Compounds **5a,b** were coupled with 2'-deoxy-3',5'-di(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl chloride **6** under alkaline conditions to afford N_3-protected nucleosides **7a,b**. Reaction of **5a,b** with chloromethyl methyl sulfide and/or 2-bromoacetaldehyde diethyl acetal in alkaline medium afforded N_3-alkyl derivatives **8a-c**. Reaction of **5a** with 1,2-dichloroethane in alkaline conditions afforded bis-thiohydantoinylethane **9a,b**. Compounds **5a,b** were condensed with formaldehyde and secondary amines to afford 3-aminomethyl-2-thiohydantoins derivatives **10a-d**. On the other hand, reaction of unsubstituted 2-thiohydantoins derivatives **11b,c** with chloromethyl methyl sulfide afforded the mono- and bis-methylthio derivatives **12a,b** and **13a,b**, respectively. Reaction of **11b,c** with secondary amines and formaldehyde gave 3-aminomethyl-2-thiohydantoins **14a-e**. Reaction of **11a-c** with bromoacetaldehyde diethyl acetal yielded the S-alkyl derivatives **15a-c** which can be hydrolysed with ethanolic hydrochloric acid to afford 5-arylidenehydantoins **16a-c**. The compounds do not display any antiviral activity.

INTRODUCTION

Several 5-arylidene-3-aryl-2-thiohydantoins and their nucleosides show potent activity against the human immunodeficiency virus (HIV),[1] the leukemia subpanel[2] and the herpes simplex virus (HSV)[3]. Moreover, cer-

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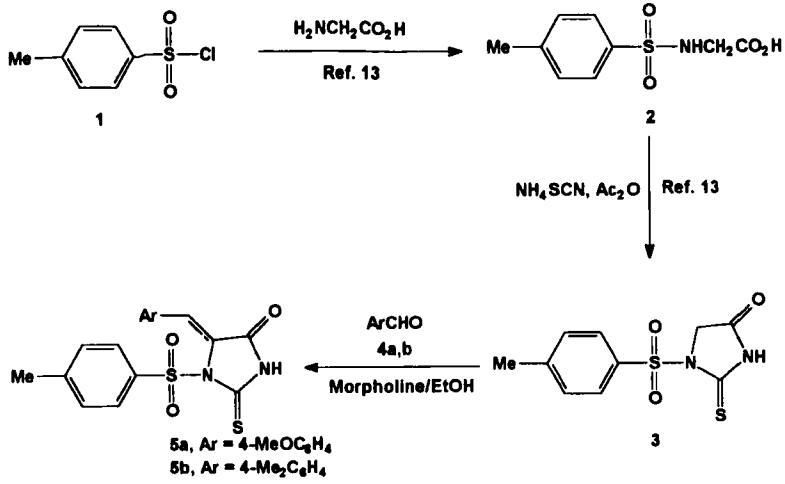
tain series of hydantoin derivatives showed interesting activities, including antiviral,[4] antiinflammatory,[5–7] anticonvulsant,[8] antidepressant,[9] and platelet inhibitory activities[10] and are a conspicuous structural feature of several inhibitors of aldose reductase.[11,12] In the course of identifying new chemical structures which may serve as leads for designing novel antiviral agents, we were particularly interested in *S*-glycosylated of 2-thiohydantions.[1–3] In this respect the linking of the latter to a saturated hydrocarbon moiety and sugar moiety were considered. We report in this paper the synthesis, reactions and conformational analysis of (*Z*)-5-arylidene-2-thiohydantoins as potential antiviral agents.

RESULTS AND DISCUSSION

1-(4-Methylphenylsulfonyl)-2-thiohydantoins **3**, which was synthesized in 2 steps in a 30% overall yield according to a reported procedure,[13] was condensed with the appropriate aromatic aldehydes in the presence of morpholine and ethanol at room temperature to afford (*Z*)-5-arylidene-1-(4-methylphenylsulfonyl)-2-thiohydantoins (**5a,b**). The structures of **5a,b** were assigned on the basis of elemental analyses and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR absorption spectrum of compound **5a** was characterized by the presence of signals for the NH, C=O and C=S groups at 2993, 1728 and 1250 cm^{-1}, respectively. The ^{1}H-NMR spectrum of compound **5a** showed a singlet at δ 7.96 ppm assigned to the vinyl proton, indicating the presence of a *Z*-configuration for the exocyclic double bond, in agreement with the ^{1}H-NMR spectra of (*E*)-5-and (*Z*)-5-arylidenehydantoin derivatives whose vinyl protons appear at δ 6.10–6.35 and 6.40–6.75 ppm,[14–16] respectively. The ^{13}C-NMR spectrum of compound **5a** showed a signal at δ 124.12 ppm assigned to the vinyl carbon, indicating the presence of a *E*-configuration for the exocyclic double bond, in agreement with the ^{13}C-NMR spectra of (*E*)-5-and (*Z*)-5-arylidenehydantoin derivatives whose vinyl protons respectively appear at δ 105–115 and 115–125 ppm[14–16] (Scheme 1).

At this stage, calculations at the AM1 level[17] were considered in order to determine the relative energies of the possible tautomeric forms. These calculations also permit the determination of the relative energies of the *E* and *Z* isomers of the arylidenehydantoin derivatives. It was found that the



SCHEME 1

Z-isomer is more stable by 3.10 kcal/mol for **5a** and thus no double bond isomerisation is anticipated. For compound **5a**, the 4 tautomeric forms α, β, γ and δ were considered. This result confirms that the exocyclic double bond must be Z. Those results show that **5a** must be present as α form and can be applied to compounds **5a,b** (Figure 1).

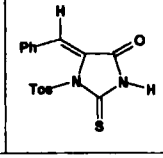
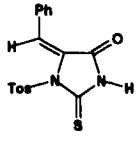
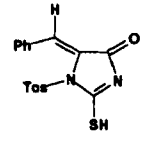
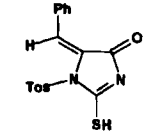
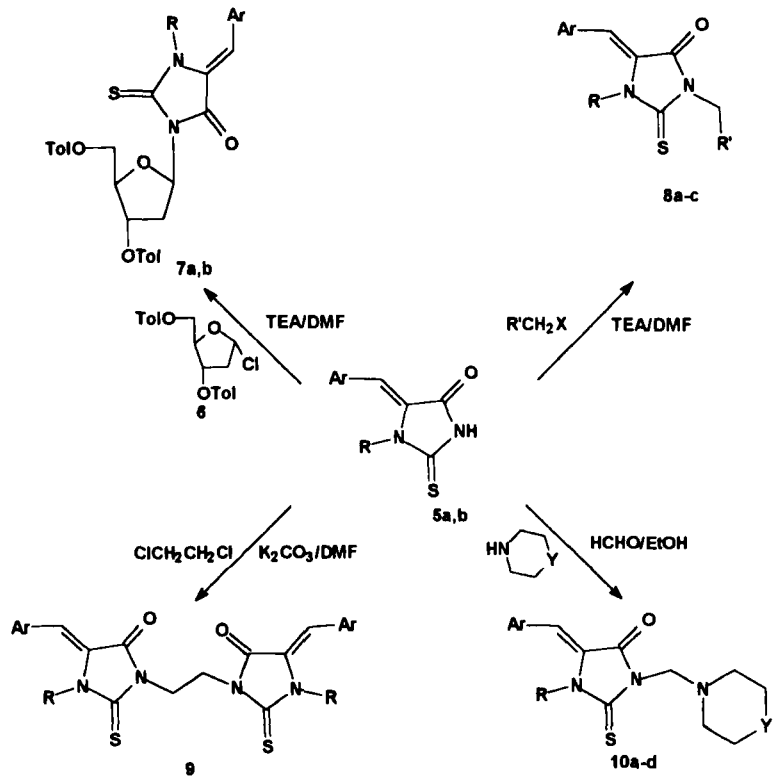
Form (ΔE kcal/mol)	α (−18.4)	β (−15.3)	γ (0)	δ (−3.6)
				

FIGURE 1 Relative energies (kcal/mol) of tautomers (α – δ) for compound **5a**

(Z)-5-arylidene-1-(4-methylphenylsulfonyl)-2-thiohydantoins (**5a,b**) were coupled with 2′-deoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl chloride (**6**) in the presence of TEA in DMF for overnight at room temperature to afford (Z)-5-arylidene-3-(2′-deoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoins (**7a,b**). Alkylation of **5a,b** with chloromethyl

methyl sulfide in DMF and anhydrous K_2CO_3 gave (*Z*)-5-arylidene-3-(methylthiomethyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoins (**8a,b**). Similarly, reaction of **5b** with 2-bromoacetaldehyde diethyl acetal in DMF and TEA yielded (*Z*)-5-(4-dimethylaminobenzylidene)-3-(2′-diethoxyethyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoin (**8c**). Treating of **5a** overnight with 1,2-dichloroethane in DMF and anhydrous K_2CO_3 at room temperature afforded 1,2-bis[5-(4-methoxybenzylidene)-1-(4-methylphenylsulfonyl)-3-(2-thiohydantoinyl)]ethane **9**. Also, treating of **5a,b** with formaldehyde and secondary amines in refluxing ethanol led to formation of (*Z*)-5-arylidene-3-(aminomethyl)-1-(4-methylphenylsulfonyl-2-thiohydantoins **10a-d**. The structures of **7–10** were assigned on the basis of elemental analyses and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR absorption spectrum of compound **8a** is characterized by the absence of a signal for the NH group and the presence of a signal at 1733 cm^{-1} due to the carbonyl group. The ^{1}H-NMR spectrum of compound **8a** showed a singlet at δ 7.75 ppm assigned to the vinyl proton. The ^{13}C-NMR spectrum of compound **8a** showed a singlet at δ 176.49 ppm assigned to the C=S group, indicating the presence of a N-3 alkylation, in agreement with the ^{13}C-NMR spectrum of (*Z*)-5-(4-methyoxybenzylidene)-1-(4-methylphenylsulfonyl)-2-thiohydantoin (**5a**), whose C=S group appears at δ 175.89 ppm (Scheme 2).

5-Arylidene-2-thiohydantoins (**11b,c**)[18] were alkylated with chloromethyl methyl sulfide in the presence of anhydrous K_2CO_3 in DMF to afford (*Z*)-5-arylidene-2-methylthiomethylthio-4-imidazolidinones (**12a,b**) and (*Z*)-5-arylidene-2,3-bis-(methylthiomethylthio)-4-imidazolidinone (**13a,b**), respectively. Compounds **11a,b**[18] were condensed with formaldehyde and secondary amines in refluxing ethanol to afford (*Z*)-5-arylidene-3-aminomethyl-2-thiohydantoins (**14a-e**). Also, compounds **11a-c** were reacted with bromoacetaldehyde diethyl acetal in DMF and anhydrous K_2CO_3 at 65°C for 3 hours to give the expected (*Z*)-5-arylidene-2-(2-diethoxyethylthio)hydantoins (**15a-c**) as the sole products. The structure assingments of **12–15** are based on elemental analyses and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR absorption spectrum of compound **15a** is characterized by the absence of signals for N_1-H and C=S groups at 3308 and 1264 cm^{-1} and the presence of a signals at 2990, 1700 cm^{-1} due to the N_3-H group and the carbonyl group. The ^{1}H-NMR spectrum of compound **15a** exhibited a singlet at δ 6.77 ppm assigned to the vinyl proton. It indicates the presence of a *Z*-configuration for the exo-

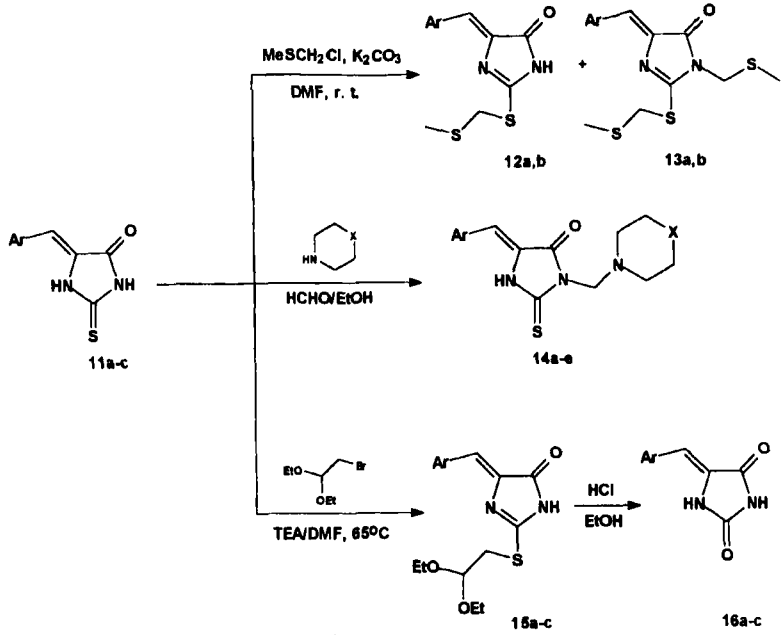


	Ar	R	Tol	R'	Y
5,7,8a	4-$MeOC_6H_4$	4-$MeC_6H_4SO_2$	4-MeC_6H_4CO	SMe	
b	4-$Me_2NC_6H_4$	4-$MeC_6H_4SO_2$	4-MeC_6H_4CO	SMe	
c	4-$Me_2NC_6H_4$	4-$MeC_6H_4SO_2$		$CH(OEt)_2$	
9	4-$MeOC_6H_4$	4-$MeC_6H_4SO_2$			
10a	4-$MeOC_6H_4$	4-$MeC_6H_4SO_2$			O
b	4-$MeOC_6H_4$	4-$MeC_6H_4SO_2$			NH
c	4-$Me_2NC_6H_4$	4-$MeC_6H_4SO_2$			O
d	4-$Me_2NC_6H_4$	4-$MeC_6H_4SO_2$			NH

SCHEME 2

cyclic double bond, in agreement with the ^{1}H-NMR spectrum of its oxygen analogue **16a**. The latter was prepared from the reaction of **15a** with 12N hydrochloric acid in refluxing ethanol. The vinyl proton of **15a** appears at δ 6.47 ppm. The ^{13}C-NMR spectrum of compound **16a** showed a signal at δ 108.35 ppm assigned to the vinyl carbon, indicating the pres-

ence of a *Z*-configuration for the exocyclic double bond. This is in agreement with the ^{13}C-NMR spectra of (*E*)-5-and (*Z*)-5-arylidenehydantoin derivatives whose vinyl protons appear at δ 105–115 and 115–125 ppm,[14–16] respectively (Scheme 3).



	Ar	X
11,15,16a	C_6H_5	
b	4-$MeOC_6H_4$	
c	4-$Me_2NC_6H_4$	
12,13,14a	4-$MeOC_6H_4$	O
b	4-$Me_2NC_6H_4$	O
c	4-$MeOC_6H_4$	NH
d	4-$Me_2NC_6H_4$	NH
e	4-$MeOC_6H_4$	CH_2

SCHEME 3

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40 °C. All melting points are uncorrected. Aluminum sheets coated with silica gel F_{254} (Merck) were used for TLC. Detection was affected by viewing under

a short-wavelength UV lamp. IR spectra were recorded with a Perkin-Elmer 1720 spectrometer. Microanalyses were performed by the Microanalysis unit, Faculty of Science, Cairo University. The NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C and on a Varian UNITY 500 NMR spectrometer at 500 MHz for ^{1}H or 125.7 MHz for ^{13}C using TMS as an internal standard and $CDCl_3$ and DMSO as solvents. Mass spectra (MS) were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer and using fast atom bombardment (FAB) on a Kratos MS 50 spectrometer. The silica gel (0.040–0.063 mm) Merck was used for the column chromatography. 1-(4-Methylphenylsulfonyl)-2-thiohydantoins (**3a,b**) were prepared according to the method of Okuda et al.[13]

(Z)-5-Arylidene-1(4-methylphenylsulfonyl)-2-thiohydantoins (5a,b)

A mixture of **1** (2.7 g, 10 mmol) and the appropriate aldehyde (10 mmol) in ethanol (30 ml) and morpholine (0.87 ml, 10 mmol) was stirred at room temperature for 24 hours until the starting material was consumed (TLC). The reaction mixture was poured into cold water and neutralised with HCl. The resulting solid was filtered off and recrystallised from ethanol to give the products **5a,b**.

(Z)-5-(4-Methoxybenzylidene)-1(4-methylphenylsulfonyl)-2-thiohydantoin (5a)

Yield 2.40 g (62 %); mp 176–178 °C. Calculated for $C_{18}H_{16}N_2O_4S_2$ (388.45): C, 55.7; H, 4.2; N, 7.2; Found: C, 55.6; H, 4.1; N, 7.3. IR (KBr): ν 2993 (NH), 1728 (C=O), 1312 (SO_2), 1250 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.39 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.99–7.96 (8H, 4d, H-Ar), 7.82 (1H, s, CH), 13.08 (1H, s, NH). ^{13}C-NMR (DMSO-d_6): δ 21.12 (CH_3), 55.37 (OCH_3), 124.12 (=CH), 113.61, 126.44, 127.91, 128.51, 129.95, 133.94, 134.30, 146.12, (C-5, C-Ar), 161.24 (C-4), 175.89 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-1-(4-methylphenylsulfonyl)-2-thiohydantoin (5b)

Yield 2.50 g (62 %); mp 193–195 °C. MS (EI); *m/z*: 401 (M^+). IR (KBr): ν 3065 (NH), 1730 (C=O), 1325 (SO_2), 1251 (C=S) cm^{-1}. ^{1}H-NMR

(DMSO-d_6): δ 2.38 (3H, s, CH_3), 3.01 (6H, s, $2CH_3$), 6.71–8.01 (8H, d, H-Ar), 7.75 (1H, s, CH), 12.89 (1H, s, NH). ^{13}C-NMR (DMSO-d_6): δ 21.07 (CH_3), 40.00 ($2CH_3$), 118.75 (=CH), 111.03, 123.25, 128.30, 129.89, 130.82, 134.19, 134.63, 145.96, 152.13 (C-5, C-Ar), 161.14 (C-4), 175.18 (C-2).

(Z)-5-Arylidene-3-(2′-deoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoins (7a,b)

The nucleobases 5a,b (10 mmol) were dissolved in dry DMF (10 ml) and 2′-deoxy-3′,5′-di(4-methylbenzoyl)-∝-D-*erythro*-pentofuranosyl chloride **6** (4.27 g, 11 mmol) portionwise with stirring. The reaction mixture was stirred overnight at room temperature, then evaporated to dryness. The residue was extracted with CH_2Cl_2 (100 ml) and chromatographed on silica gel column using ethylacetate/petroleum ether (3/7, v/v) to give the protected nucleosides **7a,b**.

(Z)-5-(4-Methoxybenzylidene)-3-(2′-deoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoin (7a)

Yield 3.50 g (47 %); mp 98–100 °C. MS (FAB, DMSO + 1 % CH_3COOH + 3-nitrobenzyl alcohol); *m/z*: 741 ($M + H^+$). IR (KBr): ν 1719 (C=O), 1598 (C=N), 1384 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.38, 2.39 (6H, 2s, $2CH_3$), 2.42 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.06 (2H, m, H-2′), 4.42 (H, m, H-5′), 4.57 (1H, m, H-4′), 5.57 (1H, m, H-3′), 6.57 (H, t, J = 5.50 Hz, H-1′), 6.92–8.11 (17H, m, =CH, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 21.54, 21.55 ($2CH_3$), 29.53 (CH_3), 33.66 (C-2′), 55.33 (OCH_3), 63.81 (C-5′), 74.72 (C-3′), 82.13 (C-4′), 83.56 (C-1′), 122.57 (=CH), 114.18, 124.20, 126.70, 128.48, 129.13, 129.21, 129.38, 129.66, 129.79, 129.91, 130.48, 134.30, 144.03, 146.28, 158.96 (C-5, C-Ar), 161.14 (C-4), 166.22, 166.25 (2C=O) and 174.21 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-(2′-deoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl)-1-(4-methylphenylsulfonyl)-2-thiohydantoin (7b)

Yield 3.70 g (49 %); mp 173–175 °C. Calculated. for $C_{40}H_{39}N_3O_8S_2$ (753.88: C, 63.7; H, 5.2; N, 5.6; Found: C, 63.4; H, 4.9; N, 5.9. MS (FAB,

DMSO + 1 % CH_3COOH + 3-nitrobenzyl alcohol); *m/z*: 754 ($M + H^+$). IR (KBr): ν 1721 (C=O), 1587 (C=N), 1372 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.41 (6H, s, $2CH_3$), 2.42 (3H, s, CH_3), 2.79 (1H, m, H-2′), 3.11 (6H, s, $2CH_3$), 4.40 (1H, m, H-5′), 4.49 (1H, m, H-4′), 5.54 (1H, m, H-3′), 6.58 (1H, t, J = 5.50 Hz, H-1′), 7.02–8.09 (17H, m, =CH, H-Ar). ^{13}C-NMR (DMSO-d_6): 20.67 ($2CH_3$), 29.50 (CH_3), 32.97 (C-2′), 39.76 ($2CH_3$), 63.19 (C-5′), 74.09 (C-3′), 80.06 (C-4′), 82.52 (C-1′), 120.47 (=CH), 113.33, 118.01, 126.44, 127.99, 128.41, 129.04, 129.21, 129.70, 132.20, 132.42, 134.52, 143.43, 145.42, 149.63, 150.69, 151.74 (C-5, C-Ar), 158.48 (C-4), 165.10, 165.25 (2C=O), 173.18 (C-2).

(Z)-5-Arylidene-1-(4-methylphenylsulfonyl)-3-(methylthiomethyl)-2-thiohydantoins (8a,b)

A mixture of **5a,b** (10 mmol) in DMF (10 ml), anhydrous K_2CO_3(1.39 g, 10 mmol) and chloromethyl methyl sulfide (0.96 g, 10 mmol) was stirred overnight at room temperature until the starting material was consumed (TLC). The reaction mixture was evaporated to dryness. The formed solid was crystallized from ethanol to give the products **8a,b**.

(Z)-5-(4-Methoxybenzylidene)-1-(4-methylphenylsulfonyl)-3-(methylthiomethyl)-2-thiohydantoin (8a)

Yield 2.20 g (49 %); mp 153–155 °C. MS (EI); *m/z*: 448 (M^+). Calculated for $C_{20}H_{20}N_2O_4S_3$ (448.56): C, 53.6; H, 4.5; N, 6.3; Found: C, 53.3; H, 4.4; N, 6.9. IR (KBr): ν 1733 (C=O), 1594 (C=N), 1380 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.29 (3H, s, CH_3), 2.43 (3H, s, SCH_3), 3.86 (3H, s, OCH_3), 4.49 (2H, s, CH_2), 7.03, 7.50 (4H, 2d, H-Ar), 7.82 (1H, s, =CH), 7.98, 8.14 (2H, 2d, H-Ar). ^{13}C- NMR (DMSO-d_6): δ 15.15 (SCH_3), 21.08 (CH_3), 38.24 (CH_2), 55.41 (OCH_3), 123.85 (=CH), 113.89, 126.20, 127.68, 129.49, 130.81, 132.58, 134.18, 147.18, 161.86 (C-5, C-Ar), 170.96 (C-4), 176.49 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-1-(4-methylphenylsulfonyl)-3-(methylthiomethyl)-2-thiohydantoin (8b)

Yield 2.30 g (50 %); m. p. 166–168 °C. MS (EI); m/z: 461. IR (KBr): ν 1699 (C=O), 1570 (C=N), 1370 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.28

(3H, s, CH_3), 2.45 (3H, s, S CH_3), 3.00 (6H, s, $2CH_3$), 4.48 (2H, s, CH_2), 6.78, 7.50 (4H, 2d, H-Ar), 7.62 (1H, s, =CH), 7.85, 8.15 (4H, 2d, H-Ar). ^{13}C- NMR (DMSO-d_6): δ 14.99 (SCH_3), 21.08 (CH_3), 38.24 (CH_2), 39.25 ($2CH_3$), 118.04 (=CH), 111.19, 122.89, 126.84, 130.25, 131.69, 133.51, 146.41, 152.84 (C-5, C-Ar), 170.67 (C-4), 174.29 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-1-(4-methylphenylsulfonyl)-3-(2′-diethoxyethyl)-2-thiohydantoin (8c)

A mixture of **5b** (4 g, 10 mmol) in DMF (10 ml), TEA (1.00 ml) and bromoacetaldehyde diethyl acetal (1.97 g, 10 mmol) was stirred at room temperature until the starting material was consumed (TLC). The reaction mixture was evaporated to dryness. The formed solid was crystallized from ethanol to give the product **8c**: Yield 2.06 g (40 %); mp 131–133 °C. MS (EI); *m/z*: 517. Calculated for $C_{25}H_{31}N_3O_5S_2$(517.65): C, 58.0; H, 6.0; N, 8.1; Found: C, 58.4; H, 6.0; N, 8.2. IR (KBr): ν 1690 (C=O), 1565 (C=N), 1375 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.18 (6H, t, J = 7.09 Hz, $2CH_3$,), 2.41 (3H, s, CH_3), 3.06 (6H, s, $2CH_3$), 3.44 (2H, d, CH_2, J = 5.08 Hz), 3.52 – 3.70 (4H, q, $2CH_2$), 4.76 (1H, t, J = 5.08 Hz, CH), 6.76, 7.50 (4H, 2d, H-Ar), 7.67 (1H, s, =CH), 7.83, 8.18 (4H, 2d, H-Ar). ^{13}C- NMR (DMSO-d_6): δ 15.05 ($2CH_3$), 21.02 (CH_3), 35.49 (CH_2), 40.00 ($2CH_3$), 61.82 ($2CH_2$), 99.59 (CH), 118.76 (=CH), 111.13, 123.67, 127.45, 130.64, 131.21, 132.80, 134.70, 146.87, 152.46 (C-5, C-Ar), 170.81 (C-4), 174.70 (C-2).

1,2-Bis[(Z)-5-(4-methoxybenzylidene)-1-(4-methylphenylsulfonyl)-2-thiohydantoinyl]ethane (9)

A mixture of **5a** (3.88 g, 10 mmol) and 1,2-dichloroethane (0.98 g, 10 mmol) was stirred overnight at room temperature until the starting material was consumed (TLC). The solvent was evaporated under vacuum to dryness. The obtained solid was crystallized from ethanol to give the product **9**: Yield 1.80 g (45 %); mp 141–143 °C. Calculated for $C_{38}H_{34}N_4O_8S_4$ (802.94): N, 7.0; Found: N, 6.8. IR (KBr): ν 1700 (C=O), 1565 (C=N), 1160 (SO_2) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.41(3H, m, CH_3), 3.83 (5H, s, OCH_3. CH_2), 6.95, 7.40 (4H, 2d, H-Ar), 7.49 (1H, s, =CH), 7.80, 8.01 (4H, 2d, H-Ar). ^{13}C-NMR: δ 21.01 (CH_3), 39.50 (CH_2),

55.21 (CH_3), 121.59 (=CH), 113.28, 126.79, 127.90, 129.44, 129.87, 133.16, 136.16, 144.47, 159.99 (C-5, C-Ar), 172.03 (C-4), 186.27 (C-2).

(Z)-5-arylidene-3-aminomethyl-1-(4-methylphenylsulfonyl)-2-thiohydantoins (10a-d)

A mixture of **5a,b** (10 mmol) and morpholine and/or piperazine (20 mmol) in ethanol (30 ml) was added to 36 % aqueous formaldehyde (2 ml, 20 mmol). The reaction mixture was heated under reflux for 7 hours until the starting material was consumed (TLC). The reaction mixture was left to cool. The resulting solid was filtered off to give the products **10a-d.**

(Z)-5-(4-Methoxybenzylidene)-3-morpholinomethyl-1-(4-methylphenylsulfonyl)-2-thiohydantoin (10a)

Yield 2.70 g (55 %); mp 185–187 °C. MS (EI); *m/z*: M^+at m/e = 487. Calculated for $C_{23}H_{25}N_3O_5S_2$ (487.58): C, 56.7; H, 5.2; N, 8.6; Found: C, 56.5; H, 5.5; N, 8.4. IR (KBr): ν 1729 (C=O), 1310 (SO_2), 1259 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.32 (4H, m, H-2′, H-6′), 2.38 (3H, s, CH_3), 3.38 (4H, m, H-3′, H-5′), 3.81 (3H, s, OCH_3), 4.58 (2H, s, CH_2), 6.99, 7.50 (4H, 2d, H-Ar), 7.88 (1H, s, =CH), 7.90, 8.01 (4H, 2d, H-Ar), ^{13}C-NMR (DMSO-d_6): δ 21.07 (CH_3), 50.81 (C-2′, C-6′), 55.41 (OCH_3), 63.03 (CH_2), 65.96 (C-3′, C-5′), 124.11 (=CH), 113.69, 128.53, 129.95, 134.14, 146.21 (C-5, C-Ar), 161.51 (C-4), 176.92 (C-2).

(Z)-5-(4-Methoxybenzylidene)-3-piperazinomethyl-1-(4-methylphenylsulfonyl)-2-thiohydantoin (10b)

Yield 3.20 g (66 %); mp 203–205 °C. IR (KBr): ν 2952 (NH), 1728 (C=O), 1310 (SO_2), 1259 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.32 (4H, m, H-2′, H-6′), 2.38 (3H, s, CH_3), 3.38 (4H, m, H-3′, H-5′), 3.81 (3H, s, OCH_3), 4.51 (2H, s, CH_2), 4.67 (1H, s, NH), 6.97–7.99 (9H, m, =CH, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 21.08 (CH_3), 50.26 (C-2′, C-6′), 55.26 (OCH_3), 62.01 (C-3′, C-5′), 124.08 (=CH), 113.65, 128.52, 129.89, 134.07, 146.11 (C-5, C-Ar), 161.45 (C-4), 175.98 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-morpholinomethyl-1-(4-methylphenylsulfonyl)-2-thiohydantoin (10c)

Yield 2.70 g (54 %); mp 145°C. MS (EI), m/z: 500. IR (KBr): ν 1718 (C=O), 1315 (SO_2), 1255 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.27 (4H, m, H-2′, H-6′), 2.37 (3H, s, CH_3), 3.03 (6H, s, $2CH_3$), 3.38 (4H, m, H-3′, H-5′), 4.58 (2H, s, CH_2), 6.74–8.06 (9H, m, =CH, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 21.03 (CH_3), 39.54 ($2CH_3$), 50.85 (C-2′, C-6′), 62.54 (CH_2), 66.04 (C-3′, C-5′), 118.54 (=CH), 111.07, 121.43, 128.30, 129.90, 133.42, 134.92, 145.76, 152.43 (C-5, C-Ar), 160.69 (C-4), 177.06 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-piperazinomethyl-1-(4-methylphenylsulfonyl)-2-thiohydantoin (10d)

Yield 2.8 g (56 %); mp 195–197°C. MS (EI), m/z: 499. Calculated for $C_{22}H_{29}N_5O_3S_2$ (499.64): C, 57.7; H, 5.9; Found: C, 57.6; H, 5.7. IR (KBr): ν 2914 (NH), 1718 (C=O), 1316 (SO_2), 1255 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.14 (4H, m, H-2′, 6′), 2.45 (3H, s, CH_3), 2.97 (3H, s, $2CH_3$), 3.22 (4H, m, H-3′, 5′), 4.69 (2H, s, N-CH_2-N), 4.98 (1H, s, NH), 6.66–8.02 (9H, m, H-Ar).

(Z)-5-Arylidene-2-(methylthiomethylthio)-4-imidazolidinones (12a,b) and (Z)-5-arylidene-2-(methylthiomethylthio)-3-(methylthiomethyl)-4-imidazolidinones (13a,b)

A mixture of **11a,b** (10 mmol) in DMF (10 ml), anhydrous K_2CO_3 (1.39 g, 10 mmol) and chloromethyl methyl sulfide (0.96 g, 10 mmol) was stirred overnight at room temperature until the starting material was consumed (TLC). The reaction mixture was evaporated to dryness. The residual solid was chromatographed on a silica gel column using ethyl acetate/petroleum ether (3/7, v/v) as eluent to afford the products **12a,b** and **13a,b**, respectively.

(Z)-5-(4-Methoxybenzylidene)-2-(methylthiomethylthio)-4-imidazolidinones (12a)

Yield 1.76 g (60 %); mp 161–163 °C. MS (EI), m/z: 294. Calculated for $C_{13}H_{14}N_2O_2S_2$ (294.38): C, 53.1; H, 4.8; N, 9.5; Found: C, 53.4; H, 5.0;

N, 9.6. IR (KBr): ν 2836 (NH), 1703 (C=O), 1567 (C=N) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.28 (3H, s, SCH_3), 3.85 (3H, s, OCH_3), 4.58 (2H, s, CH_2), 6.78 (1H, s, =CH), 7.03 (2H, d, H-Ar) and 8.20 (2H, d, H-Ar). ^{13}C- NMR (DMSO-d_6): δ 15.05 (SCH_3), 36.29 (CH_2), 55.21 (OCH_3), 121.58 (=CH), 114.30, 127.05, 133.45, 137.46, 160.60 (C-5, C-Ar), 162.54 (C-4), 170.97 (C-2).

(*Z*)-5-(4-Methoxybenzylidene)-2-(methylthiomethylthio)-3-(methylthiomethyl)-4-imidazolidinone (13a)

Yield 1.00 g (28 %); mp 127–129 °C. IR (KBr): ν 2916 (NH), 1699 (C=O), 1590 (C=N). ^{1}H-NMR (DMSO-d_6): δ 2.12, 2.24 (6H, s, $2CH_3$), 3.80 (3H, s, CH_3), 4.61, 4.67 (4H, s, $2CH_2$), 6.91 (1H, s, =CH), 6.99 (2H, d, H-Ar), 8.20 (2H, d, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 14.60, 15.23 (2 SCH_3), 36.43 (CH_2), 42.88 (CH_2), 55.30 (OCH_3), 124.10 (CH), 114.45, 126.76, 133.95, 135.62 (C-5, C-Ar), 161.07 (C-4), 168.62 (C-2).

(*Z*)-5-(4-Dimethylaminobenzylidene)-2-(methylthiomethylthio)-4-imidazolidinone (12b)

Yield 1.84 g (60 %); mp 118–120 °C. MS (EI), m/z: 307. IR (KBr): ν 1708 (C=O), 1598 (C=N). ^{1}H-NMR (DMSO-d_6): δ 2.21 (3H, s, CH_3), 3.98 (3H, s, CH_3), 4.50 (2H, s, CH_2), 6.66 (1H, s, =CH), 6.71 (2H, d, H-Ar), 8.02 (2H, d, H-Ar), 11.55 (1H, s, NH). ^{13}C-NMR (DMSO-d_6): δ 16.02 (SCH_3), 35.18 (CH_2), 39.54 ($2CH_3$), 121.06 (=CH), 111.76, 123.35, 133.48, 135.35, 150.74 (C-5, C-Ar), 159.33 (C-4), 170.62 (C-2).

(*Z*)-5-(4-Dimethylaminobenzylidene)-2-(methylthiomethylthio)-3-(methylthiomethyl)-4-imidazolidinone (13b)

Yield 1.1 g (30 %); mp 189–191 °C. IR (KBr): ν 1694 (C=O), 1591 (C=N). ^{1}H-NMR (DMSO-d_6): δ 2.11 (3H, s, SCH_3), 2.23 (3H, s, SCH_3), 3.00 (6H, s, NMe_2), 4.59, 4.65 (4H, 2s, $2CH_2$), 6.73 (2H, d, H-Ar), 6.84 (1H, s, =CH), 8.08 (2H, d, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 14.57, 15.21 (2 SCH_3), 36.31 (CH_2), 39.53 ($2CH_3$), 42.74 (CH_2), 111.77 (CH), 121.43, 125.81, 133.23, 134.01, 151.87 (C-5, C-Ar), 161.08 (C-4), 168.60 (C-2).

(Z)-5-Arylidene-3-morpholinomethyl-2-thiohydantoins (14a-e)

A mixture of **11a-c** (10 mmol) and morpholine and/or piperazine and/or piperidine (20 mmol) in ethanol (30 ml) was added to 36 % aqueous formaldehyde (2 ml, 20 mmol). The reaction mixture was heated under reflux for 7 hours until the starting material was consumed (TLC). The reaction mixture was left to cool. The resulting solids were filtered off to give the products **14a-e**.

(Z)-5-(4-Methoxybenzylidene)-3-morpholinomethyl-2-thiohydantoin (14a)

Yield 2.49 g (75 %); mp 181–183 °C. MS (EI), *m/z*: 333. Calculated for $C_{16}H_{19}N_3O_2S$ (333.40): C, 57.6; H, 5.7; N, 12.6; Found: C, 58.0; H, 6.0; N, 12.6. IR (KBr): ν 2956 (NH), 1729 (C=O), 1286 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.57 (4H, m, H-2′, H-6′), 3.51 (4H, m, H-3′, H-5′), 3.79 (3H, s, OCH_3), 4.67 (2H, s, CH_2), 6.57 (1H, s, =CH), 6.95 (2H, d, H-Ar), 7.73 (2H, d, H-Ar), 12.30 (1H, s, N_1-H). ^{13}C-NMR (DMSO-d_6): δ 51.14 (C-2′, C-6′), 55.31 (OCH_3), 61.95 (CH_2), 66.06 (C-3′, C-5′), 113.51, 114.44, 124.12, 124.90, 132.41, 160.55 (=CH, C-5, C-Ar), 165.32 (C-4), 179.62 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-morpholinomethyl-2-thiohydantoin (14b)

Yield 2.42 g (70 %); mp 203–205°C. MS (EI), *m/z*: 346. IR (KBr): ν 2853 (NH), 1723 (C = O), 1288 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.58 (4H, s, H-2′, H-6′), 2.98 (6H, s, $2CH_3$), 3.50 (4H, m, H-3′, H-5′), 4.66 (2H, s, CH_2), 6.53 (1H, s, =CH), 6.71 (2H, d, H-Ar), 7.67 (2H, d, H-Ar), 12.15 (1H, s, N_1-H). ^{13}C-NMR (DMSO-d_6): δ 39.56 ($2CH_3$), 51.20 (C-2′, C-6′), 61.82 (CH_2), 66.07 (C-3′, C-5′), 111.84, 115.60, 119.51, 121.50, 132.53, 151.15 (=CH, C-5, C-Ar), 165.23 (C-4), 178.23 (C-2).

(Z)-5-(4-Methoxybenzylidene)-3-piperazinomethyl-2-thiohydantoin (14c)

Yield 1.66 g (50 %); mp 251–253°C. IR (KBr): ν 2946 (NH), 1728 (C=O), 1261 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.57 (4H, m, H-2′, H-6′), 3.30

(4H, m, H-3′, H-5′), 3.79 (3H, s, OCH_3), 4.63 (1H, s, CH_2), 6.53 (1H, s, =CH), 6.44, 8.01 (4H, 2d, H-Ar), 11.99 (1H, s, N_1-H). ^{13}C-NMR(DMSO-d_6): δ 35.69 (C-3′, C-5′), 50.63 (C-2′, C-6′), 55.29 (OCH_3), 61.69 (CH_2), 113.23, 124.12, 126.12, 132.37, 160.43, 162.43 (=CH, C-5, C-Ar), 166.03 (C-4), 178.79 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-piperazinomethyl-2-thiohydantoin (14d)

Yield 1.7 g (50 %); mp 248–250 °C. Calculated for $C_{17}H_{23}N_5OS$ (345.46): C, 59.1; H, 6.7; N, 20.3; Found: C, 59.2; H, 6.6; N, 20.1. IR (KBr): ν 2943 (NH), 1726 (C=O), 1291 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.29 – 2.86 (8H, m, H-2′, H-3′, H-5′, H-6′), 2.96 (6H, s, $2CH_3$), 4.59 (2H, s, CH_2), 6.39 (1H, s, =CH), 6.49 – 8.02 (4H, m, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 35.25 (C-2′, C-6′), 39.43 ($2CH_3$), 50.68 (C-3′, C-5′), 61.54 (CH_2), 111.83, 114.11, 119.64, 123.77, 132.25, 151.01 (=CH, C-5, C-Ar), 166.01 (C-4), 177.41 (C-2).

(Z)-5-(4-Dimethylaminobenzylidene)-3-piperidinomethyl-2-thiohydantoin (14e)

Yield 2.58 g (75 %); mp 212–214°C. MS (EI), *m/z*: 344. IR (KBr): ν 2932 (NH), 1718 (C=O), 1285 (C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.41 (6H, m, H-2′, H-4′, H-6′), 2.56 (4H, m, H-3′, H-5′), 2.98 (6H, s, $2CH_3$), 4.65 (2H, s, CH_2), 6.51 (1H, s, =CH), 6.71 (2H, d, H-Ar), 7.66 (2H, d, H-Ar), 12.09 (1H, s, N_1-H). ^{13}C-NMR (DMSO-d_6): δ 23.38 (C-2′, C-6′), 25.47 (C-3′, C-5′), 39.58 ($2CH_3$), 51.99 (C-4′), 62.61 (CH_2), 111.84, 115.29, 119.60, 121.73, 132.47, 151.10 (=CH, C-5, C-Ar), 165.35 (C-4), 178.50 (C-2).

(Z)-5-Arylidene-2-(2-diethoxyethylthio)-4-imidazolidinone (15a-c)

A mixture of **11a-c** (10 mmol) and anhydrous K_2CO_3 (1.39 g, 10 mmol) in DMF (10 ml) was added to 2-bromoacetaldehyde diethyl acetal (10 mmol). The mixture was stirred at 65 °C for 3 hours until the starting material was consumed (TLC). The reaction mixture was poured in cold

water. Upon scratching a solid formed and was filtered off and crystallized from methanol to give the products **15a-c.**

(*Z*)-5-(4-Benzylidene)-2-(2-diethoxyethylthio)-4-imidazolidinone (15a)

Yield 1.44 g (45 %); mp 136–138 °C. MS (EI), *m/z*: 320. Calculated for $C_{16}H_{20}N_2O_3S$ (320.40) C, 60.0; H, 6.3; N, 8.7; Found: C, 60.2; H, 5.9; N, 8.5. IR (KBr): ν 2990 (NH), 1700 (C=O), 1625 (C=N) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.16 (6H, t, J = 6.99 Hz, $2CH_3$), 3.46 (2H, d, J = 5.24 Hz, SCH_2), 3.55, 3.70 (4H, 2q, J = 6.98 Hz, $2CH_2$), 4.81 (1H, t, J = 5.35 Hz, CH), 6.77 (1H, s, =CH), 7.40–8.19 (5H, m, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 15.09 ($2CH_3$), 32.58 (SCH_2), 62.17 ($2CH_2$), 100.56 (CH), 120.83 (=CH), 128.59, 129.59, 131.46, 134.38, 139.25 (C-5, C-Ar), 164.85 (C-4), 170.76 (C-2).

(*Z*)-5-(4-Methoxybenzylidene)-2-(2-diethoxyethylthio)-4-imidazolidin one (15b)

Yield 1.4 g (40 %); mp 128–130 °C. IR (KBr): ν 2980 (NH), 1710 (C=O), 1580 (C=N) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.16 (6H, t, J = 7.09 Hz, $2CH_3$), 3.45 (2H, d, J = 5.35 Hz, SCH_2), 3.54, 3.70 (4H, 2q, J = 7.10 Hz, $2CH_2$), 3.81 (3H, s, OCH_3), 4.79 (1H, t, J = 5.41 Hz, CH), 6.69 (1H, s, =CH), 6.96 (2H, d, H-Ar), 8.16 (2H, d, H-Ar). ^{13}C-NMR (DMSO-d_6): δ 15.11 ($2CH_3$), 32.52 (SCH_2), 55.19 (OCH_3), 62.11 ($2CH_2$), 100.69 (CH), 120.37 (=CH), 114.15, 127.33, 133.20, 128.14, 160.38 (C-5, C-Ar), 164.52 (C-4), 171.88 (C-2).

(*Z*)-5-(4-Dimethylaminobenzylidene)-2-(2-diethoxyethylthio)-4-imidazolidinone (15c)

Yield 1.45 g (40 %); mp 183–185 °C. MS (EI), *m/z*: 363. IR (KBr): ν 3000 (NH), 1675 (C=O), 1560 (C=N) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.19 (6H, t, J = 7.04 Hz, $2CH_3$), 3.03 (6H, s, $2CH_3$), 3.46 (2H, d, J = 5.19 Hz, SCH_2), 3.57, 3.73 (4H, 2q, J = 7.04 Hz, $2CH_2$), 4.82 (1H, t, J = 4.96 Hz, CH), 6.71 (1H, s, =CH), 6.75 (2H, d, H-Ar), 8.08 (2H, d, H-Ar), 11.64 (1H, s, N_3-H). ^{13}C-NMR: 15.14 ($2CH_3$), 32.47 (SCH_2), 39.52 ($2CH_3$),

62.14 ($2CH_2$), 100.68 (CH), 121.81(=CH), 111.56, 123.02, 133.40, 135.37, 151.13 (C-5, C-Ar), 159.75 (C-4), 170.70 (C-2).

(Z)-5-Arylidenehydantoin (16a-c)

A mixture of **15a-c** (10 mmol) and 1N hydrochloric acid in ethanol (10 ml) was heated under reflux for 1 hour until the starting material was consumed (TLC). The solid obtained was collected and recrystallized from MeOH to give the products **16a-c**.

(Z)-5-Benzylidenehydantoin (16a)

Yield 1.10 g (58 %); mp 218–220 °C. ^{1}H-NMR (DMSO-d_6): δ 6.47 (1H, s, =CH), 7.37–7.68 (5H, m, H-Ar), 10.60 (1H, s, N_1-H) and 11.32 (1H, s, N_3-H). ^{13}C-NMR (DMSO-d_6): δ 108.35 (=CH), 128.06, 128.45, 128.89, 129.65, 133.05 (C-5, C-Ar), 155.83 (C-2), 165.79 (C-4).

(Z)-5-(4-Methoxybenzylidene)hydantoin (16b)

Yield 1.30 g (59 %); mp 240–242 °C. ^{1}H-NMR (DMSO-d_6): δ 3.76 (3H, s, OCH_3), 6.36 (1H, s, =CH), 6.91, 7.57 (4H, 2d, H-Ar), 10.40 (1H, s, N_1-H) and 11.13 (1H, s, N_3-H). ^{13}C-NMR (DMSO-d_6): δ 55.22 (OCH_3), 108.76 (=CH), 114.37, 125.55, 126.19, 130.87, 131.51, 159.61 (C-5, C-Ar), 155.61 (C-2), 165.79 (C-4).

(Z)-5-(4-Dimethylaminobenzylidene)hydantoin (16c)

Yield 1.50 g (65 %); mp 262–264 °C. MS (EI), m/z: 231. ^{1}H-NMR (DMSO-d_6): δ 2.92 (6H, s, $2CH_3$), 6.33 (1H, s, =CH), 6.66, 7.47 (4H, 2d, H-Ar), 10.23 (1H, s, N_1-H) and 11.01 (1H, s, N_3-H). ^{13}C-NMR (DMSO-d_6): δ 39.43 ($2CH_3$), 110.10 (=CH), 111.73, 120.09, 123.70, 130.79, 131.41, 150.04 (C-5, C-Ar), 155.40 (C-2), 165.56 (C-4).

Acknowledgements

The authors would like to express their gratitude and thanks to Prof. Claus Nielsen, Department of Virology, Statens Seruminstitut, Artillerive 5, DK-2300 Copenhagen, Denmark, for carrying out the antiviral testing of

the prepared compounds and Danish International Development Agency (DANIDA) for the facilities provided throughout this work.

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