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# SYNTHESIS OF 3-SUBSTITUTED 5-ARYLIDENE-1-METHYL-2-THIOHYDANTOINS UNDER MICROWAVE IRRADIATION

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**Abstract** - A mono-modal microwave oven was used to expedite the synthesis of small libraries of 3-substituted 1-methyl-2-thiohydantoins and 3-substituted 5-arylidene-1-methyl-2-thiohydantoins. In comparison with the traditional reflux methods, similar or higher yields were obtained.

## INTRODUCTION

The pioneering reports on the use of microwave irradiation as thermal source to carry out organic reactions were published in 1986.[1,2] In 1989, the first review dealing with microwave heating in organic synthesis appeared.[3] Since then a rapidly increasing number of reports and reviews have been published demonstrating that a large variety of organic reactions can be conducted safely in microwave ovens leading to reduction in reaction times of up to three orders of magnitude.[4,5] These reports also include solid-phase reactions and the generation of combinatorial libraries.[6] The timesaving ability together with the very short response times and the minimization of thermal decomposition of products are the main advantages of microwave heating.

In our efforts to generate combinatorial libraries of potentially biologically active compounds using expeditious parallel synthesis, we have been interested in a series of heterocyclic compounds. Among these are the substituted thiohydantoins whereof several 5-arylidene-2-thiohydantoins have shown potent activity against herpes simplex virus (HSV),[7] human immunodeficiency virus (HIV)[8] and the leukemia sub-panel.[9] In addition, certain other series of hydantoin derivatives showed interesting activities, including antiviral,[10] anti-inflammatory,[11] anticonvulsant,[12] antidepressant,[13] and platelet inhibitor

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activities.[14] Furthermore, they are a conspicuous structural feature of several inhibitors of aldose reductase.[15,16] Our interest in 2-thiohydantoins prompted us to test the role of microwave irradiation on the preparation of 3-substituted 1-methyl-2-thiohydantoins and 3-substituted 5-arylidene-1-methyl-2-thiohydantoins as potential antiviral and antitumor agents. Multi-component reactions (MCR), where three or more reactants combine to give a single product, have lately received much attention and were also considered.[17] Thus, retrosynthetic analysis showed that 3-substituted 5-arylidene-1-methyl-2-thiohydantoins (**3**-**6**) could be prepared using two different strategies (Figure 1). Path A relies on the Knoevenagel-type condensation of an aldehyde with 3-substituted 1-methyl-2-thiohydantoins (**2**), which can be obtained by reaction of an isothiocyante derivative (**1**) with sarcosine.[18] Alternatively, as outlined by path B, the reaction can be carried out as a one-pot three-component condensation reaction of aldehydes, isothiocyante derivatives (**1**) and sarcosine.

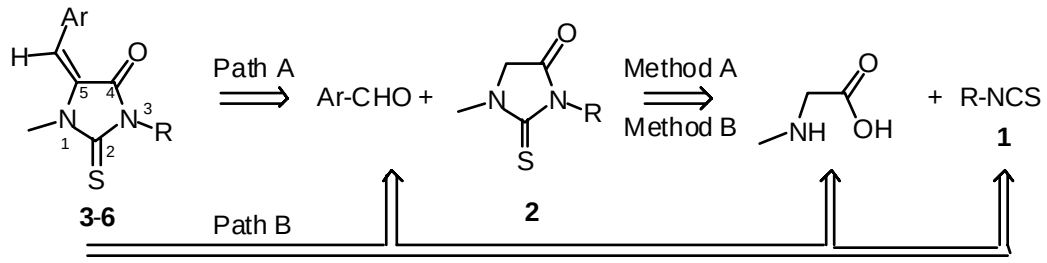


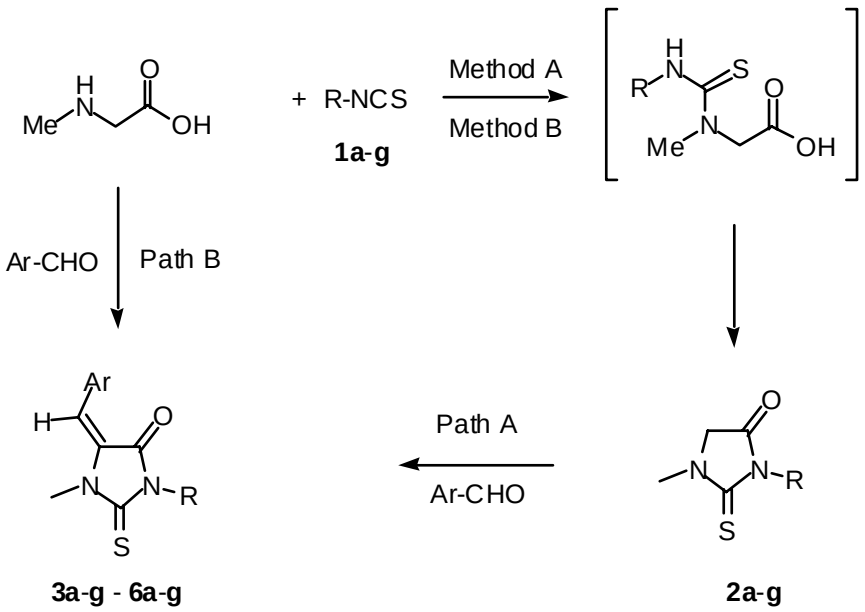

**Figure 1**

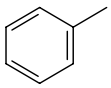
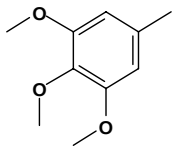
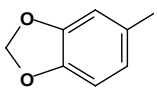
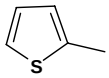
3-Substituted 5-arylidene-1-methyl-2-thiohydantoins (**3**-**6**, numbering shown) are available by two routes: (A) Two-step synthesis *via* 3-substituted 1-methyl-2-thiohydantoins (**2**) followed by a Knoevenagel-type condensation of aldehydes. (B) One-pot reaction *via* three-component condensation of aldehydes, isothiocyante derivatives (**1**) and sarcosine. Method A and method B refer to microwave irradiation and thermal reflux, respectively.

## RESULTS AND DISCUSSION

Herein, we report the results of several experiments in which organic reactions have been carried out in Teflon-sealed glass vessels heated by mono-modal microwave irradiation under moderate pressure.[19] In most cases the high temperature readily obtained in the reaction vessels led to remarkable rate enhancements and therefore an inherent dramatic reduction in reaction times. The present work describes the synthesis and configurations of a library of previously unreported series of 3-substituted 1-methyl-2-thiohydantoins (**2a-**

**g**) and 3-substituted 5-arylidene-1-methyl-2-thiohydantoins (**3a-g** to **6a-g**). Four aldehydes and seven isothiocyanates were used, giving rise to a small library of 28 different products




| 1-3 | R | Ar | | R | Ar |
|---|---|---|---|---|---|
| **a** | *Methyl* |  | **5a** | *Methyl* |  |
| **b** | *Phenyl* | | **b** | *Phenyl* | |
| **c** | *Allyl* | | **c** | *Allyl* | |
| **d** | *n-Butyl* | | **d** | *n-Butyl* | |
| **e** | *n-Hexyl* | | **e** | *n-Hexyl* | |
| **f** | *Cyclohexylmethyl* | | **f** | *Cyclohexylmethyl* | |
| **g** | *2-(4-Morpholino)ethyl* | | **g** | *2-(4-Morpholino)ethyl* | |
| **4a** | *Methyl* |  | **6a** | *Methyl* |  |
| **b** | *Phenyl* | | **b** | *Phenyl* | |
| **c** | *Allyl* | | **c** | *Allyl* | |
| **d** | *n-Butyl* | | **d** | *n-Butyl* | |
| **e** | *n-Hexyl* | | **e** | *n-Hexyl* | |
| **f** | *Cyclohexylmethyl* | | **f** | *Cyclohexylmethyl* | |
| **g** | *2-(4-Morpholino)ethyl* | | **g** | *2-(4-Morpholino)ethyl* | |

**Scheme 1**

(Scheme 1). First, path A was implemented. The condensation of aromatic aldehydes with 3-substituted 1-methyl-2-thiohydantoins (**2a**-**g**) was accomplished by reflux in a solution of triethylamine and ethanol under either microwave irradiation (method A) or traditional reflux methods (method B).

Likewise, intermediates (**2a**-**g**) were prepared from sarcosine and the appropriate isothiocyanates (**1a**-**h**) by either microwave irradiation or reflux in ethanol. In addition, reaction path B was implemented. The multi-component reaction of aromatic aldehydes, the appropriate isothiocyanates and sarcosine was performed by heating a solution of ethanol containing triethylamine under either microwave irradiation or traditional reflux. Yields resulting from the different synthetic approaches are given in Table 1.

**TABLE 1** Yields of **3a**-**6g** from the different synthetic approaches.

| | **Yields (Path A) (%)** | | **Yields (Path B) (one pot, %)** | | | **Yields (Path A) (%)** | | **Yields (Path B) (one pot, %)** | |
|---|---|---|---|---|---|---|---|---|---|
| **Method** | A | B | A | B | **Method** | A | B | A | B |
| **3a** | 86 | 93 | 78 | 70 | **5a** | 82 | 90 | 77 | 68 |
| **3b** | 88 | 92 | 84 | 80 | **5b** | 94 | 98 | 88 | 86 |
| **3c** | 92 | 90 | 71 | 69 | **5c** | 84 | 92 | 78 | 66 |
| **3d** | 86 | 84 | 73 | 65 | **5d** | 80 | 82 | 70 | 64 |
| **3e** | 86 | 85 | 71 | 68 | **5e** | 84 | 86 | 69 | 65 |
| **3f** | 84 | 80 | 74 | 67 | **5f** | 84 | 92 | 78 | 72 |
| **3g** | 83 | 86 | 74 | 70 | **5g** | 84 | 92 | 80 | 78 |
| **4a** | 83 | 88 | 74 | 72 | **6a** | 84 | 88 | 70 | 68 |
| **4b** | 90 | 92 | 85 | 87 | **6b** | 94 | 98 | 88 | 86 |
| **4c** | 86 | 93 | 82 | 88 | **6c** | 94 | 98 | 86 | 88 |
| **4d** | 82 | 85 | 78 | 69 | **6d** | 82 | 90 | 78 | 74 |
| **4e** | 87 | 91 | 80 | 74 | **6e** | 86 | 92 | 80 | 72 |
| **4f** | 90 | 96 | 83 | 79 | **6f** | 90 | 94 | 86 | 78 |
| **4g** | 86 | 92 | 78 | 72 | **6g** | 86 | 94 | 76 | 74 |

The structures of **3a**-**g** to **6a**-**g** were confirmed on the basis of spectral data (IR, $^{1}$H-NMR, $^{13}$C-NMR and MS) and elemental analysis. The IR absorption spectrum of compound (**3a**) was characterized by the presence of a signal at 1717 cm$^{-1}$ due to the carbonyl group as well as the thiocarbonyl group at 1230 cm$^{-1}$. The $^{1}$H-NMR spectrum of compound (**3a**) showed a singlet at $\delta$ 6.48 ppm assigned to the vinyl proton, indicating the presence of an

*E*-configuration for the exocyclic double bond. This is in agreement with the $^{1}$H-NMR spectra of 5-(*E*)- and 5-(*Z*)-arylidenehydantoin derivatives whose vinyl protons appear at $\delta$ 6.10-6.50 and 6.50-6.75 ppm, respectively.[20,21] The $^{13}$C-NMR spectrum of compound (**3a**) showed an absorbtion at $\delta$ 120.60 ppm assigned to the vinyl group, likewise indicating the presence of an *E*-configuration for the exocyclic double bond, in agreement with the $^{13}$C-NMR spectra of 5-(*Z*)- and 5-(*E*)-arylidenehydantoin derivatives whose vinyl groups appear at $\delta$ 105-115 and 115-125 ppm, respectively.[20] Further evidence for the *E*-configuration came from nuclear Overhauser effect (NOE) experiments on compound (**3a**). On irradiation of the $CH_3$ resonance 3.63 ppm, a large NOE enhancement was found for the *ortho* protons of the phenyl group (11%) and on irradiation of the *ortho* protons a small NOE enhancement was found for $CH_3$ (3%).

In conclusion, two small libraries have been synthesized consisting of 7 different 3-substituted 1-methyl-2-thiohydantoins and 28 different 5-arylidene-1-methyl-2-thiohydantoins, using either microwave irradiation or traditional reflux. Yields were generally very high for both reaction paths, but microwave reactions were completed within a few minutes as compared to hours required for reflux conditions.

## EXPERIMENTAL

**General Method:** $^{1}$H-NMR (300.13 MHz) and $^{13}$C-NMR (75.47 MHz) spectra were measured on a Bruker Advance DPX 300 machine using tetramethylsilane as external reference. Analytical data were obtained using a C,H,N Elemental analyzer Carlo Erba 1106. MS was recorded on a Finnigan MAT-INCOS 500 spectrometer with ionization by electron impact (70 eV). Melting points were uncorrected. Alumina sheets coated with silica gel 60 $F_{254}$ (Merck) were used for TLC and compounds were visualized by UV-irradiation of the fluorescent TLC plates. IR spectra were measured on a Nicolet Magna 750. Column chromatography was performed with silica gel 60 mesh ASTM (Merck)**.** The microwave oven used for the experiments was a Microwell 10 from Labwell AB (now Personal Chemistry AB, Uppsala, Sweden). The oven is mono-modal and the effect can be adjusted within 1W intervals between 1 and 500 W.

### 3-substituted 1-methyl-2-thiohydantoins (2a-g)

***Method A:*** *N*-Methylglycine (89 mg, 1 mmol), the appropriate isothiocyanate **(1a-g**; 1.1 mmol), and ethanol (3 mL) were placed in a Teflon-sealed glass vessel (10 mL capacity) and introduced in a microwave cavity at 60 watts at 120-125°C and 2.50-3.50 Bar for 12 min. The reaction mixture was allowed to reach rt. The reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography eluting with $Et_2O$/petroleum ether (1:1, v/v) to give products (**2a-g**).

***Method B:*** The same amounts of reactants indicated in method A were heated under reflux for 12 h. The resulting hydantoins were isolated as indicated in the method described above.

**1,3-Dimethyl-2-thiohydantoin (2a):** Using methyl isothiocyanate (73 mg, 1 mmol), method A afforded 120 mg (83%) of **2a** and 100 mg (69%) were obtained following method B. mp 90-92°C (lit.,[22] 92.0-92.5°C). IR (KBr): ν 1720 (C=O), 1225 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.24 (3H, s, N(3)-$CH_3$), 3.33 (3H, s, N(1)-$CH_3$), 4.00 (2H, s, H-5).

**1-Methyl-3-phenyl-2-thiohydantoin (2b):** Using phenyl isothiocyanate (135 mg, 1 mmol), method A afforded 185 mg (90%) of **2b** and 190 mg (92%) were obtained following method B. mp 160-162°C (lit.,[18] 163°C). IR (KBr): ν 1717 (C=O), 1226 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.37 (3H, s, N(1)-$CH_3$), 4.20 (2H, s, H-5), 7.27-7.52 (5H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 34.23 ($CH_3$), 54.21 (C-5), 128.25, 129.02, 129.07, 133.33 (C-Ar), 169.54 (C-4), 183.07 (C-2).

**3-Allyl-1-methyl-2-thiohydantoin (2c):** Using allyl isothiocyanate (99 mg, 1 mmol), method A afforded 136 mg (80%) of **2c** (red oil) and 123 mg (72%) were obtained following method B. IR (KBr): ν 1722 (C=O), 1228 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.32 (3H, s, N(1)-$CH_3$), 4.01 (3H, s, H-5), 4.14 (2H, 2 x t, J = 1.35 Hz, N(3)-$CH_2$), 5.23 (2H, m, =$CH_2$), 5.86 (1H, m, CH). Anal. Calcd for $C_7H_{10}N_2OS$: C, 49.4, H, 5.9; N, 16.5. Found: C, 49.6; H, 6.2; N, 16.8.

**3-*n*-Butyl-1-methyl-2-thiohydantoin (2d):** Using n-butyl isothiocyanate (115 mg, 1 mmol), method A afforded 143 mg (77%) of **2d** (red oil) and 127 mg (68%) were obtained following method B. IR (KBr): ν 1720 (C=O), 1230 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.94 (3H, m, $CH_3$), 1.44-1.78 (4H, m, 2 x $CH_2$), 3.29 (3H, s, N(1)-$CH_3$), 3.97 (2H, s, H-5). $^{13}$C-NMR ($CDCl_3$): δ 13.77 ($CH_3$), 20.08 ($CH_2$), 29.79 ($CH_2$), 34.04 ($CH_3$), 42.08 ($CH_2$), 53.88 (C-5), 170.42 (C-4), 183.50 (C-2). Anal. Calcd for $C_8H_{14}N_2OS$: C, 51.6, H, 7.6; N, 15.0. Found: C, 51.6; H, 7.2; N, 14.8.

**3-*n*-Hexyl-1-methyl-2-thiohydantoin (2e):** Using n-hexyl isothiocyanate (143 mg, 1 mmol), method A afforded 161 mg (75%) of **2e** (red oil) and 150 mg (70%) were obtained following method B. IR (KBr): ν 1714 (C=O), 1227 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.84 (3H, t, J = 7.52 Hz, $CH_3$), 1.26 (6H, m, $3CH_2$), 1.65 (2H, m, $CH_2$), 3.53 (3H, s, N(1)-$CH_3$), 3.86 (2H, t, J = 7.54 Hz, N(3)-$CH_2$), 4.00 (2H, s, H-5). Anal. Calcd for $C_{10}H_{18}N_2OS$: C, 56.0, H, 8.5; N, 13.1. Found: C, 56.2; H, 8.2; N, 12.8.

**3-Cyclohexylmethyl-1-methyl-2-thiohydantoin (2f):** Using cyclohexylmethyl isothiocyanate (155 mg, 1 mmol), method A afforded 176 mg (78%) of **2f** (red oil) and 152 mg (67%) were obtained following method B. IR (KBr): ν 1712 (C=O), 1229 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.20-1.25 (6H, m, H-3, H-4, H-$5_{cyclohexane}$), 1.70 (4H, m, H-2, H-$6_{cyclohexane}$), 2.00 (1H, m, H-$1_{cyclohexane}$), 3.63 (3H, s, N(1)-$CH_3$), 3.76 (2H, d, J = 7.45 Hz, N(3)-$CH_2$), 3.96 (2H, s, H-5). Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.4, H, 8.0; N, 12.4. Found: C, 58.2; H, 8.2; N, 12.7.

**3-(2-(4-Morpholino)ethyl)-1-methyl-2-thiohydantoin (2g):** Using 2-(4-morpholino)ethyl isothiocyanate (172 mg, 1 mmol), method A afforded 207 mg (85%) of **2g** and 199 mg (82%) were obtained following method B. mp 74-76°C. IR (KBr): ν 1720 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 2.52 (4H, t, J = 4.5 Hz, H-2', H-6'), 2.64 (2H, t, J = 13.5 Hz, N-$CH_2$), 3.33 (3H, s, N(1)-$CH_3$), 3.65 (4H, t, J = 4.5 Hz, H-3', H-5'), 3.94 (2H, t, J = 13.5 Hz, N(3)-$CH_2$), 4.01 (2H, s, H-5). Anal. Calcd for $C_{10}H_{17}N_3O_2S$: C, 49.4, H, 7.0; N, 17.3. Found: C, 49.3; H, 7.2; N, 17.7.

**5-(*E*)-Arylidene-3-substituted 1-methyl-2-thiohydantoins (3a-g to 6a-g)**

***Path A: Method A:*** 3-Substituted 1-methyl-2-thiohydantoins (**2a-g**, 1 mmol), the appropriate aromatic aldehydes **(**1.1 mmol), morpholine (87 μL, 1 mmol) and ethanol (3 mL) were placed in a Teflon-sealed glass vessel (10 mL capacity) and introduced in a microwave cavity at 60 watts at 150-155°C and 3.50-5.00 Bar for 12 min. The reaction mixture was allowed to reach rt. The reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography with $Et_2O$/petroleum ether (1:1, v/v) to give products (**3a-g**/**6a-g**) in quantitative yields.

***Path A: Method B:*** The same amounts of reactants indicated in method A were heated at 40-50 $^oC$ for 12 h. The resulting 2-thiohydantoins were isolated as indicated in the method described above.

***Path B: Method A:*** *N*-Methylglycine (89 mg, 1 mmol), the appropriate isothiocyanates **(1a-g**; 1.1 mmol) and the appropriate aromatic aldehydes **(**1.1 mmol), triethylamine (202 μL, 2 mmol) and ethanol (3 mL) were placed in a Teflon-sealed glass vessel (10 mL capacity) and introduced in a microwave cavity at 60 watts at 150-155°C and 3.50-5.00 Bar for 20 min. The reaction mixture was allowed to reach to rt. The reaction mixture was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography with $Et_2O$/petroleum ether (1:1, v/v) to give products (**3a-g**/**6a-g**) in quantitative yields.

***Path B: Method A:*** The same amounts of reactants indicated in method A were heated under reflux for 6 h. The resulting 2-thiohydantoins were isolated as indicated in the method described above.

**5-((*E*)-Benzylidene)-1,3-Dimethyl-2-thiohydantoin (3a):** Using path A, method A afforded 200 mg (86%) of **3a** and 216 mg (93%) were obtained following method B. Using path B, method A afforded 181 mg (78%) of **3a** and 162 mg (70%) were obtained following method B. mp 140-142°C (lit.,[18] 144°C). IR (KBr): ν 1717 (C=O), 1230 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.38 (3H, s, N(3)-$CH_3$), 3.63 (3H, s, N(1)-$CH_3$), 6.48 (1H, s, =CH), 7.41 (3H, m, H-Ar), 7.98 (2H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 28.28 (N(3)-$CH_3$), 30.60 (N(1)-$CH_3$), 120.60 (=CH), 128.45, 129.21, 129.97, 130.80, 132.02 (C-5, C-Ar), 161.64 (C-4), 177.35 (C-2).

**5-((*E*)-Benzylidene)-1-methyl-3-phenyl-2-thiohydantoin (3b):** Using path A, method A afforded 259 mg (88%) of **3b** and 270 mg (92%) were obtained following method B. Using path B, method A afforded 247 mg (84%) of **3b** and 235 mg (80%) were obtained following method B. mp 192-194°C (lit.,[18] 196°C). IR (KBr): ν 1720 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.71 (3H, s, N(1)-$CH_3$), 6.58 (1H, s, =CH), 7.34-8.03 (10H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 30.88 ($CH_3$), 121.06 (=CH), 128.45, 128.49, 128.98, 129.13, 129.18, 130.10, 130.95, 131.91, 133.30 (C-Ar), 161.24 (C-4), 176.80 (C-2).

**3-Allyl-5-((*E*)-benzylidene)-1-methyl-2-thiohydantoin (3c):** Using path A, method A afforded 237 mg (92%) of **3c** and 232 mg (90%) were obtained following method B. Using path B, method A afforded 184 mg (71%) of **3c** and 178 mg (69%) were obtained following method B. mp 153-155°C (yellow crystals). IR (KBr): ν 1719 (C=O), 1234 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.60 (3H, s, N(1)-$CH_3$), 4.46 (2H, 2 x t, J = 1.35 Hz, N(3)-$CH_2$), 5.24 (2H,

m, = $CH_2$), 5.84 (1H, m, CH), 6.48 (1H, s, =CH), 7.42 (3H, m, H-Ar), 7.97 (2H, m, H-Ar). Anal. Calcd for $C_{14}H_{14}N_2OS$: C, 65.1, H, 5.5; N, 10.8. Found: C, 65.0; H, 5.2; N, 10.8.

**5-((*E*)-Benzylidene)-3-*n*-butyl-1-methyl-2-thiohydantoin (3d):** Using path A, method A afforded 236 mg (86%) of **3d** and 230 mg (84%) were obtained following method B. Using path B, method A afforded 200 mg (73%) of **3d** and 178 mg (65%) were obtained following method B. mp 104-106°C. IR (KBr): ν 1714 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.94 (3H, m, $CH_3$), 1.40-1.70 (4H, 2m, 2 x $CH_2$), 3.60 (3H, s, N(1)-$CH_3$), 3.95 (2H, t, J = 7.5 Hz, N(3)-$CH_2$), 6.48 (1H, s, =CH), 7.42 (3H, m, H-Ar), 7.96 (2H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 13.68 ($CH_3$), 20.05 ($CH_2$), 29.82 ($CH_2$), 30.71 (N(1)-$CH_3$), 41.78 (N(3)-$CH_2$), 120.23 (=CH), 128.30, 129.13, 129.78, 130.67, 131.97, (C-5, C-Ar), 161.49 (C-4), 176.90 (C-2). Anal. Calcd for $C_{15}H_{18}N_2OS$: C, 65.7, H, 6.6; N, 10.2. Found: C, 65.5; H, 6.9; N, 10.0.

**5-((*E*)-Benzylidene)-3-*n*-hexyl-1-methyl-2-thiohydantoin (3e):** Using path A, method A afforded 335 mg (86%) of **3e** and 231 mg (85%) were obtained following method B. Using path B, method A afforded 277 mg (71%) of **3e** and 265 mg (68%) were obtained following method B. mp 153-155°C. IR (KBr): ν 1715 (C=O), 1230 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.80 (3H, t, J = 7.5 Hz, $CH_3$), 1.20 (6H, m, 3$CH_2$), 1.62 (2H, m, $CH_2$), 3.50 (3H, s, N(1)-$CH_3$), 3.82 (2H, t, J = 7.5 Hz, N(3)-$CH_2$), 6.35 (1H, s, =CH), 7.38 (3H, m, H-Ar), 7.98 (2H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 14.26 ($CH_3$), 22.76 ($CH_2$), 26.73 ($CH_2$), 27.97 ($CH_2$), 30.72 (N(1)-$CH_3$), 31.63 (N(1)-$CH_2$), 42.32 (N(3)-$CH_2$), 120.51 (=CH), 128.60, 129.45, 130.07, 130.96, 132.27, (C-5, C-Ar), 161.76 (C-4), 177.20 (C-2). MS, *m/z* = 302 ($M^+$). Anal. Calcd for $C_{17}H_{22}N_2OS$: C, 67.5, H, 7.3; N, 9.3. Found: C, 67.5; H, 7.6; N, 9.2.

**5-((*E*)-Benzylidene)-3-cyclohexylmethyl-1-methyl-2-thiohydantoin (3f):** Using path A, method A afforded 264 mg (84%) of **3f** and 251 mg (80%) were obtained following method B. Using path B, method A afforded 232 mg (74%) of **3f** and 210 mg (67%) were obtained following method B. mp 92-94°C. IR (KBr): ν 1710 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.20-1.24 (6H, m, H-3, H-4, H-$5_{cyclohexane}$), 1.68 (4H, m, H-2, H-$6_{cyclohexane}$), 1.95 (1H, m, H-$1_{cyclohexane}$), 3.60 (3H, s, N(1)-$CH_3$), 3.77 (2H, d, J = 7.5 Hz, N(3)-$CH_2$), 6.47 (1H, s, =CH), 7.40 (3H, m, H-Ar), 7.98 (2H, m, H-Ar). MS, *m/z* = 314 ($M^+$). Anal. Calcd for $C_{18}H_{22}N_2OS$: C, 68.8, H, 7.1; N, 8.9. Found: C, 68.7; H, 7.4; N, 9.1.

**5-((*E*)-Benzylidene)-3-[2-(4-morpholino)ethyl]-1-methyl-2-thiohydantoin (3g):** Using path A, method A afforded 275 mg (83%) of **3g** and 285 mg (86%) were obtained following

method B. Using path B, method A afforded 245 mg (74%) of **3g** and 232 mg (70%) were obtained following method B. mp 180-182°C. IR (KBr): ν 1714 (C=O), 1230 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 2.47 (4H, t, J = 4.5 Hz, H-2', H-6'), 2.60 (2H, t, J = 6.9 Hz, N-$CH_2$), 3.50 (3H, s, N(1)-$CH_3$), 3.59 (4H, t, J = 4.5 Hz, H-3', H-5'), 3.98 (2H, t, J = 6.9 Hz, N(3)-$CH_2$), 6.39 (1H, s, =CH), 7.29-7.91 ( 5H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 30.50 (N(1)-$CH_3$), 38.72 (N-$CH_2$), 53.60 (C-2', C-6'), 55.43 (C-3', C-5'), 66.91 (N(3)-$CH_2$), 120.39 (=CH), 128.33, 129.03, 129.82, 130.64, 131.93, (C-5, C-Ar), 161.44 (C-4), 176.72 (C-2). Anal. Calcd for $C_{17}H_{21}N_3O_2S$: C, 61.6, H, 6.4; N, 12.7. Found: C, 61.3; H, 6.2; N, 12.7.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-1,3-dimethyl-2-thiohydantoin (4a):** Using path A, method A afforded 229 mg (83%) of **4a** and 243 mg (88%) were obtained following method B. Using path B, method A afforded 204 mg (74%) of **4a** and 200 mg (72%) were obtained following method B. mp 198-200°C. IR (KBr): ν 1717 (C=O), 1230 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.38 (3H, s, N(3)-$CH_3$), 3.62 (3H, s, N(1)-$CH_3$), 5.98 (2H, s, $CH_2$), 6.46 (1H, s, =CH), 7.35 (2H, d, J = 7.25 Hz, H-Ar), 7.95 (1H, s, H-Ar). Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.5; H, 4.4; N, 10.1. Found: C, 56.6; H, 4.5; N, 10.4.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-1-methyl-3-phenyl-2-thiohydantoin (4b):** Using path A, method A afforded 304 mg (90%) of **4b** and 311 mg (92%) were obtained following method B. Using path B, method A afforded 287 mg (85%) of **4b** and 294 mg (87%) were obtained following method B. mp 262-264°C. IR (KBr): ν 1718 (C=O), 1233 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.70 (3H, s, N(1)-$CH_3$), 6.00 (2H, s, $OCH_2O$), 6.51 (1H, s, =CH), 6.81-8.02 (8H, m, H-Ar). Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.9, H, 4.2; N, 8.3. Found: C, 69.1; H, 5.0; N, 9.6.

**3-Allyl-5-((*E*)-3,4-methylenedioxybenzylidene)-1-methyl-2-thiohydantoin (4c):** Using path A, method A afforded 260 mg (86%) of **4c** and 281 mg (93%) were obtained following method B. Using path B, method A afforded 248 mg (82%) of **4c** and 266 mg (88%) were obtained following method B. mp 142-144°C. IR (KBr): ν 1720 (C=O), 1231 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.62 (3H, s, N(1)-$CH_3$), 4.56 (2H, 2 x t, J = 1.34 Hz, N(3)-$CH_2$), 5.23 (2H, m, = $CH_2$), 5.87 (1H, m, CH), 6.00 (2H, s, $CH_2$), 6.48 (1H, s, =CH), 7.48 (2H, m, H-Ar), 8.00 (1H, s, H-Ar). Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.6; H, 4.7; N, 9.3. Found: C, 59.9; H, 4.5; N, 9.3.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-3-*n*-butyl-1-methyl-2-thiohydantoin (4d):** Using path A, method A afforded 261 mg (82%) of **4d** and 270 mg (85%) were obtained

following method B. Using path B, method A afforded 248 mg (78%) of **4d** and 219 mg (69%) were obtained following method B. mp 143-145°C. IR (KBr): ν 1714 (C=O), 1228 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.95 (3H, m, $CH_3$), 1.40-1.70 (4H, 2m, 2 x $CH_2$), 3.62 (3H, s, N(1)-$CH_3$), 3.96 (2H, t, J = 7.52 Hz, N(3)-$CH_2$), 6.00 (2H, s, $CH_2$), 6.48 (1H, s, =CH), 7.48 (2H, s, H-Ar), 7.98 (1H, s, H-Ar). Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.4, H, 5.7; N, 8.8. Found: C, 60.3; H, 5.9; N, 8.5.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-3-*n*-hexyl-1-methyl-2-thiohydantoin (4e):** Using path A, method A afforded 301 mg (87%) of **4e** and 315 mg (91%) were obtained following method B. Using path B, method A afforded 277 mg (80%) of **4e** and 256 mg (74%) were obtained following method B. mp 120-122°C. IR (KBr): ν 1713 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.80 (3H, t, J = 7.5 Hz, $CH_3$), 1.25 (6H, m, 3$CH_2$), 1.61 (2H, m, $CH_2$), 3.55 (3H, s, N(1)-$CH_3$), 3.92 (2H, t, J = 7.5 Hz, N(3)-$CH_2$), 5.98 (2H, s, $CH_2$), 6.35 (1H, s, =CH), 7.35 (2H, 2d, J = 7.3 Hz, H-Ar), 7.94 (1H, s, H-Ar). Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 62.4, H, 6.4; N, 8.1. Found: C, 62.3; H, 6.5; N, 8.0.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-3-cyclohexylmethyl-1-methyl-2-thiohydantoin (4f):** Using path A, method A afforded 322 mg (90%) of **4f** and 343 mg (96%) were obtained following method B. Using path B, method A afforded 297 mg (83%) of **4f** and 283 mg (79%) were obtained following method B. mp 160-162°C. IR (KBr): ν 1712 (C=O), 1228 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.00-1.24 (6H, m, H-3, H-4, H-$5_{cyclohexane}$), 1.65 (4H, m, H-2, H-$6_{cyclohexane}$), 1.96 (1H, m, H-$1_{cyclohexane}$), 3.60 (3H, s, N(1)-$CH_3$), 3.78 (2H, d, J = 7.5 Hz, N(3)-$CH_2$), 6.02 (2H, s, $CH_2$), 6.40 (1H, s, =CH), 6.84 (1H, d, J = 8.1 Hz, H-Ar), 7.36 (1H, d, J = 8.1 Hz, H-Ar), 7.98 (1H, s, H-Ar). Anal. Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.7, H, 6.2; N, 7.8. Found: C, 63.5; H, 6.5; N, 7.6.

**5-((*E*)-3,4-Methylenedioxybenzylidene)-3-[2-(4-morpholino)ethyl]-1-methyl-2-thiohydantoin (4g):** Using path A, method A afforded 348 mg (86%) of **4g** and 372 mg (92%) were obtained following method B. Using path B, method A afforded 316 mg (78%) of **4g** and 292 mg (72%) were obtained following method B. mp 163-165°C. IR (KBr): ν 1717 (C=O), 1230 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 2.48 (4H, t, J = 4.5 Hz, H-2', H-6'), 2.64 (2H, t, J = 6.9 Hz, N-$CH_2$), 3.52 (3H, s, N(1)-$CH_3$), 3.60 (4H, t, J = 4.5 Hz, H-3', H-5'), 4.00 (2H, t, J = 6.9 Hz, N(3)-$CH_2$), 6.02 (2H, s, $CH_2$), 6.40 (1H, s, =CH), 6.84 (1H, d, J = 8.1 Hz, H-Ar), 7.36 (1H, d, J = 8.1 Hz, H-Ar), 7.98 (1H, s, H-Ar). Anal. Calcd for $C_{20}H_{26}N_3O_4S$: C, 59.4, H, 6.5; N, 10.4. Found: C, 59.3; H, 6.2; N, 10.7.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-1,3-dimethyl-2-thiohydantoin (5a):** Using path A, method A afforded 264 mg (82%) of **5a** and 290 mg (90%) were obtained following method B. Using path B, method A afforded 248 mg (77%) of **5a** and 219 mg (68%) were obtained following method B. mp 141-143°C. IR (KBr): ν 1712 (C=O), 1233 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.38 (3H, s, N(3)-$CH_3$), 3.62 (3H, s, N(1)-$CH_3$), 3.86, 3.90 (9H, 2s, 3 x $OCH_3$), 6.50 (1H, s, =CH), 7.41 (3H, m, H-Ar), 7.50 (2H, m, H-Ar). Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.6; N, 8.7. Found: C, 55.7; H, 5.5; N, 8.5.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-3-phenyl-1-methyl-2-thiohydantoin (5b):** Using path A, method A afforded 361 mg (94%) of **5b** and 376 mg (98%) were obtained following method B. Using path B, method A afforded 338 mg (88%) of **5b** and 330 mg (86%) were obtained following method B. mp 198-200°C. IR (KBr): ν 1718 (C=O), 1230 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.74 (3H, s, N(1)-H), 3.92, 3.93 (9H, 2s, 3 x $OCH_3$), 6.52 (1H, s, =CH), 7.36-7.54 (7H, m, H-Ar). $^{13}$C-NMR ($CDCl_3$): δ 31.08 ($CH_3$), 56.51, 61.11 (3 x OMe), 122.02 (=CH), 109.01, 127.60, 128.40, 128.73, 129.31, , 129.40, 133.53, 140.42, 153.03 (C-Ar), 161.42 (C-4), 176.45 (C-2). Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.5, H, 5.2; N, 7.3. Found: C, 62.3; H, 4.9; N, 7.2.

**3-Allyl-5-((*E*)-3,4,5-trimethoxybenzylidene)-1-methyl-2-thiohydantoin (5c):** Using path A, method A afforded 292 mg (84%) of **5c** and 320 mg (92%) were obtained following method B. Using path B, method A afforded 271 mg (78%) of **5c** and 229 mg (66%) were obtained following method B. mp 176-178°C. IR (KBr): ν 1712 (C=O), 1232 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.62 (3H, s, N(1)-$CH_3$), 3.88, 3.91 (9H, 2s, 3 x $OCH_3$), 4.56 (2H, 2 x t, J = 1.35 Hz, N(3)-$CH_2$), 5.23 (2H, m, = $CH_2$), 5.87 (1H, m, CH), 6.48 (1H, s, =CH), 7.48 (2H, s, H-Ar). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.6; H, 5.8; N, 8.0. Found: C, 58.7; H, 5.5; N, 8.3.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-3-*n*-butyl-1-methyl-2-thiohydantoin (5d):** Using path A, method A afforded 291 mg (80%) of **5d** and 298 mg (82%) were obtained following method B. Using path B, method A afforded 255 mg (70%) of **5d** and 233 mg (64%) were obtained following method B. mp 164-166°C. IR (KBr): ν 1717 (C=O), 1230 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 0.95 (3H, m, $CH_3$), 1.40-1.70 (4H, 2m, 2 x $CH_2$), 3.62 (3H, s, N(1)-$CH_3$), 3.88, 3.91 (9H, 2s, 3 x $OCH_3$), 3.96 (2H, t, J = 7.52 Hz, N(3)-$CH_2$), 6.46 (1H, s, =CH), 7.47 (2H, m, H-Ar). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.3, H, 6.6; N, 7.7. Found: C, 59.2; H, 6.9; N, 7.5.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-3-*n*-hexyl-1-methyl-2-thiohydantoin (5e):** Using path A, method A afforded 329 mg (84%) of **5e** and 337 mg (86%) were obtained following method B. Using path B, method A afforded 270 mg (69%) of **5e** and 255 mg (65%) were obtained following method B. mp 153-55°C. IR (KBr): ν 1713 (C=O), 1234 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 0.81 (3H, t, J = 7.6 Hz, $CH_3$), 1.25 (6H, m, $3CH_2$), 1.60 (2H, m, $CH_2$), 3.62 (3H, s, N(1)-$CH_3$), 3.98 (11H, m, N(3)-$CH_2$, 3 x $OCH_3$), 6.38 (1H, s, =CH), 7.45 (2H, s, H-Ar). MS, *m/z* = 392 ($M^+$). Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.2, H, 7.2; N, 7.1. Found: C, 61.0; H, 6.9; N, 7.3.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-3-cyclohexylmethyl-1-methyl-2-thiohydantoin (5f):** Using path A, method A afforded 355 mg (84%) of **5f** and 372 mg (92%) were obtained following method B. Using path B, method A afforded 315 mg (78%) of **5f** and 291 mg (72%) were obtained following method B. mp 138-140°C. IR (KBr): ν 1714 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 1.20-1.25 (6H, m, H-3, H-4, H-$5_{cyclohexane}$), 1.66 (4H, m, H-2, H-$6_{cyclohexane}$), 1.97 (1H, m, H-$1_{cyclohexane}$), 3.62 (3H, s, N(1)-$CH_3$), 3.78 (2H, d, J = 7.52 Hz, N(3)-$CH_2$), 3.98 (11H, m, N(3)-$CH_2$, 3 x $OCH_3$), 6.40 (1H, s, =CH), 7.46 (2H, s, H-Ar). Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.4, H, 7.0; N, 6.9. Found: C, 62.2; H, 6.9; N, 7.2.

**5-((*E*)-3,4,5-Trimethoxybenzylidene)-3-[2-(4-morpholino)ethyl]-1-methyl-2-thiohydantoin (5g):** Using path A, method A afforded 353 mg (84%) of **5g** and 378 mg (92%) were obtained following method B. Using path B, method A afforded 337 mg (80%) of **5g** and 328 mg (78%) were obtained following method B. mp 103-105°C. IR (KBr): ν 1710 (C=O), 1232 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 2.48 (4H, t, J = 4.5 Hz, H-2', H-6'), 2.65 (2H, t, J = 6.9 Hz, N-$CH_2$), 3.51 (3H, s, N(1)-$CH_3$), 3.62 (4H, t, J = 4.5 Hz, H-3', H-5'), 3.98 (9H, m, 3 x $OCH_3$), 4.00 (2H, t, J = 6.9 Hz, N(3)-$CH_2$), 6.40 (1H, s, =CH), 7.48 (2H, s, H-Ar). Anal. Calcd for $C_{20}H_{27}N_3O_5S$: C, 57.0, H, 6.5; N, 10.0. Found: C, 57.3; H, 6.2; N, 9.7.

**1,3-Dimethyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6a):** Using path A, method A afforded 200 mg (84%) of **6a** and 209 mg (88%) were obtained following method B. Using path B, method A afforded 166 mg (70%) of **6a** and 162 mg (68%) were obtained following method B. mp 188-190°C. IR (KBr): ν 1712 (C=O), 1234 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): δ 3.35 (3H, s, N(3)-$CH_3$), 3.64 (3H, s, N(1)-$CH_3$), 6.64 (1H, s, =CH), 7.05 (1H, t, J = 4.2 Hz, H-4'), 7.45 (1H, d, J = 5.2 Hz, H-3'), 7.66 (1H, d, J = 3.0 Hz, H-5'). Anal. Calcd for $C_{10}H_{10}N_2OS_2$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.6; H, 4.2; N, 10.5.

**1-Methyl-3-phenyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6b):** Using path A, method A afforded 361 mg (94%) of **6b** and 376 mg (98%) were obtained following method B. Using path B, method A afforded 338 mg (88%) of **6b** and 330 mg (86%) were obtained following method B. mp 253-255°C. IR (KBr): ν 1716 (C=O), 1230 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.73 (3H, s, N(1)-$CH_3$), 6.70 (1H, s, =CH), 7.10-7.73 (8H, m, H-Ar). Anal. Calcd for $C_{15}H_{12}N_2OS_2$: C, 60.0, H, 4.0; N, 9.3. Found: C, 60.3; H, 3.9; N, 9.2.

**3-Allyl-1-methyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6c):** Using path A, method A afforded 248 mg (94%) of **6c** and 259 mg (98%) were obtained following method B. Using path B, method A afforded 227 mg (86%) of **6c** and 232 mg (88%) were obtained following method B. mp 167-169°C. IR (KBr): ν 1715 (C=O), 1228 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 3.55 (3H, s, N(1)-$CH_3$), 4.53 (2H, 2 x t, J = 1.5 Hz, N(3)-$CH_2$), 5.27 (2H, m, = $CH_2$), 5.84 (1H, m, CH), 6.65 (1H, s, =CH), 7.05 (1H, t, J = 4.2 Hz, H-4'), 7.48 (1H, d, J = 5.2 Hz, H-3'), 7.70 (1H, d, J = 3.0 Hz, H-5'). $^{13}$C-NMR ($CDCl_3$): δ 30.71 (N(1)-$CH_3$), 44.18 (C-$3_{allyl}$), 113.26 (=CH), 118.78 (C-$1_{allyl}$), 126.26 (C-$2_{allyl}$), 127.97 (C-5), 131.04, 131.99, 135.40, 135.82 (C-Ar), 161.57 (C-4), 175.85 (C-2). Anal. Calcd for $C_{12}H_{12}N_2OS_2$: C, 54.5; H, 4.6; N, 10.6. Found: C, 54.2; H, 4.7; N, 10.4.

**3-*n*-Butyl-1-methyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6d):** Using path A, method A afforded 230 mg (82%) of **6d** and 252 mg (90%) were obtained following method B. Using path B, method A afforded 218 mg (78%) of **6d** and 207 mg (74%) were obtained following method B. mp 133-135°C. IR (KBr): ν 1713 (C=O), 1229 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 0.96 (3H, m, $CH_3$), 1.40-1.72 (4H, 2m, 2 x $CH_2$), 3.60 (3H, s, N(1)-$CH_3$), 3.98 (2H, t, J = 7.5 Hz, N(3)-$CH_2$), 6.64 (1H, s, =CH), 7.04 (1H, t, J = 4.3 Hz, H-4'), 7.46 (1H, d, J = 5.22 Hz, H-3'), 7.65 (1H, d, J = 3.1 Hz, H-5'). Anal. Calcd for $C_{13}H_{16}N_2OS_2$: C, 55.7; H, 5.8; N, 10.0. Found: C, 55.5; H, 5.7; N, 10.3.

**3-*n*-Hexyl-1-methyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6e):** Using path A, method A afforded 265 mg (86%) of **6e** and 283 mg (92%) were obtained following method B. Using path B, method A afforded 246 mg (80%) of **6e** and 222 mg (72%) were obtained following method B. mp 106-108°C. IR (KBr): ν 1710 (C=O), 1226 (C=S) $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$): δ 0.79 (3H, t, J = 7.5 Hz, $CH_3$), 1.23 (6H, m, 3$CH_2$), 1.62 (2H, m, $CH_2$), 3.51 (3H, s, N(1)-$CH_3$), 3.82 (2H, t, J = 7.5 Hz, N(3)-$CH_2$), 6.73 (1H, s, =CH), 7.03 (1H, t, J = 4.2 Hz, H-4'), 7.46 (1H, d, J = 5.1 Hz, H-3'), 7.67 (1H, d, J = 3.0 Hz, H-5'). $^{13}$C-NMR ($CDCl_3$): δ 13.11 ($CH_3$), 21.51 ($CH_2$), 23.63 ($CH_2$), 25.47 ($CH_2$), 30.38 (N(1)-$CH_3$), 42.80 ($CH_2$),

112.06 (=CH), 125.10 (C-5), 126.71, 130.56, 134.27, 134.73, (C-Ar), 160.64 (C-4), 178.00 (C-2). Anal. Calcd for $C_{15}H_{20}N_2OS_2$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.3; H, 6.5; N, 9.2.

**3-Cyclohexylmethyl-1-methyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6f):** Using path A, method A afforded 288 mg (90%) of **6f** and 301 mg (94%) were obtained following method B. Using path B, method A afforded 275 mg (86%) of **6f** and 249 mg (78%) were obtained following method B. mp 160-162°C. IR (KBr): $\nu$ 1714 (C=O), 1228 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): $\delta$ 0.98-1.23 (6H, m, H-3, H-4, H-$5_{cyclohexane}$), 1.68 (4H, m, H-2, H-$6_{cyclohexane}$), 1.96 (1H, m, H-$1_{cyclohexane}$), 3.59 (3H, s, N(1)-$CH_3$), 3.80 (2H, d, J = 7.2 Hz, N(3)-$CH_2$), 6.69 (1H, s, =CH), 7.10 (1H, dd, J = 3.90, 5.1 Hz, H-4'), 7.51 (1H, d, J = 4.8 Hz, H-3'), 7.73 (1H, d, J = 3.9 Hz, H-5'). Anal. Calcd for $C_{16}H_{20}N_2OS_2$: C, 60.0; H, 6.3; N, 8.7. Found: C, 58.9; H, 6.1; N, 8.4.

**3-(2-(4-Morpholino)ethyl)-1-methyl-5-((*E*)-2-thienylidene)-2-thiohydantoin (6g):** Using path A, method A afforded 290 mg (86%) of **6g** and 317 mg (94%) were obtained following method B. Using path B, method A afforded 256 mg (76%) of **6g** and 249 mg (74%) were obtained following method B. mp 204-206°C. IR (KBr): $\nu$ 1712 (C=O), 1234 (C=S) $cm^{-1}$. $^1$H-NMR ($CDCl_3$): $\delta$ 2.46 (4H, t, J = 4.5 Hz, H-2', H-6'), 2.62 (2H, t, J = 6.9 Hz, N-$CH_2$), 3.50 (3H, s, N(1)-$CH_3$), 3.62 (4H, t, J = 4.5 Hz, H-3', H-5'), 3.98 (2H, t, J = 6.9 Hz, N(3)-$CH_2$), 6.68 (1H, s, =CH), 7.10 (1H, dd, J = 3.90, 5.1 Hz, H-4'), 7.50 (1H, d, J = 4.8 Hz, H-3'), 7.72 (1H, d, J = 3.9 Hz, H-5'). MS, *m/z* = 337 ($M^+$). Anal. Calcd for $C_{15}H_{19}N_3O_2S_2$: C, 53.4, H, 5.7; N, 12.5. Found: C, 53.3; H, 5.5; N, 12.7.

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