

This article was downloaded by:

On: 27 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

## Microwave-Assisted Synthesis of Some Novel Thiazolidinone and Thiohydantoin Derivatives of Isatins

Dushyant Singh Raghuvanshi<sup>a</sup>; Krishna Nand Singh<sup>a</sup>

<sup>a</sup> Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi, India

Online publication date: 05 November 2010

**To cite this Article** Raghuvanshi, Dushyant Singh and Singh, Krishna Nand(2010) 'Microwave-Assisted Synthesis of Some Novel Thiazolidinone and Thiohydantoin Derivatives of Isatins', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 185: 11, 2243 — 2248

**To link to this Article:** DOI: 10.1080/10426500903567554

**URL:** <http://dx.doi.org/10.1080/10426500903567554>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## MICROWAVE-ASSISTED SYNTHESIS OF SOME NOVEL THIAZOLIDINONE AND THIOHYDANTOIN DERIVATIVES OF ISATINS

Dushyant Singh Raghuvanshi and Krishna Nand Singh

Department of Chemistry, Faculty of Science, Banaras Hindu University,  
Varanasi, India

*A simple, rapid, and efficient method for the synthesis of some new thiazolidinone and thiohydantoin derivatives of isatins along with some Mannich bases has been achieved in excellent yield from indole-2,3-dione-3-thiosemicarbazone employing microwave irradiation.*

**Keywords** Isatin; Mannich base; microwave; Schiff base; thiazolidinone; thiohydantoin

### INTRODUCTION

Microwave-assisted organic synthesis has currently emerged as a fascinating and clean methodology in synthetic organic chemistry.<sup>1</sup> Isatin derivatives are endowed with a variety of biological activities such as antibacterial, antifungal, antiplasmodial, and anti-HIV activity.<sup>2–5</sup> Schiff and Mannich bases of 1*H*-indole-2,3-dione have been found to exhibit a broad spectrum of chemotherapeutic properties including antiviral, antitubercular, antifungal, and antibacterial activity.<sup>6–9</sup> An insight into the structure–activity relationships of isatins reveals a profound increase in the biological activities of *N*-Mannich bases and 3-thiosemicarbazones of 5-bromo-isatin.<sup>10–15</sup> The hydantoin structure motifs display a wide range of biological activities, such as antiarrhythmic, anticonvulsant, antiepileptic, antineuralgic, trigeminal neuralgia, and skeletal muscle relaxant activity.<sup>16–18</sup> Further, 4-thiazolidinones have been reported to be highly effective as antimicrobial, antiviral, anticancer, and thrombolytic drugs.<sup>19,20</sup> It may be anticipated that the combination of the thiazolidinone and thiohydantoin moieties placed at suitable positions of the isatin framework would remarkably enhance the biological activity. Taking this into consideration, an efficient and safe synthesis of some new indole systems containing the thiazolidinone and thiohydantoin moieties has been developed using microwave irradiation.

### RESULTS AND DISCUSSION

A number of synthetic methods for the formation of Mannich and Schiff bases have been described during the past two decades, but they usually suffer from drawbacks such as

Received in final form on 15 December 2009.

The authors are thankful to UGC, New Delhi, India, for financial assistance.





Address correspondence to Krishna Nand Singh, Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India. E-mail: knsinghbhu@yahoo.co.in

harsh reaction conditions, lack of versatility, use of corrosive reagents, long reaction times, and tedious workup procedures. Therefore, the search for an easy and efficient method for the preparation of *N*-Mannich bases, thiohydantoins, and thiazolidinones is always desirable. With the current focus on green chemistry, carrying out organic synthesis under microwave irradiation is an important goal in clean synthesis. As a result, we report in this article a practical and efficient alternative for the synthesis of thiohydantoins, thiazolidinones, and *N*-Mannich bases by the use of microwave irradiation. In the present study, 1*H*-indole-2,3-dione **1a** and its 5-bromo derivative **1b** were reacted with thiosemicarbazide in ethanol containing a catalytic amount of glacial acetic acid in a household microwave oven at 160 W to give the thiosemicarbazone derivatives **2a** and **2b**, respectively. Compounds **2** were subsequently allowed to undergo a Mannich reaction using formaldehyde solution and morpholine, piperidine, or diethyl amine in ethanol to furnish the Mannich bases **3a–e** in good yields. The 2-(isatin-3-azino)-4-thiazolidinones **4a,b** were prepared by the reaction of **2a,b** with chloroacetic acid in ethanol containing anhydrous sodium acetate, whereas the 3-(isatin-3-imino)-2-thiohydantoins **5a,b** were obtained by the reaction of **2a,b** with chloroacetic acid in the presence of piperidine (Scheme 1). All products displayed IR spectra as well as <sup>1</sup>H and <sup>13</sup>C NMR spectra consistent with the assigned structures. The yields of the compounds **2–5** and their melting points are given in Table I.

## EXPERIMENTAL

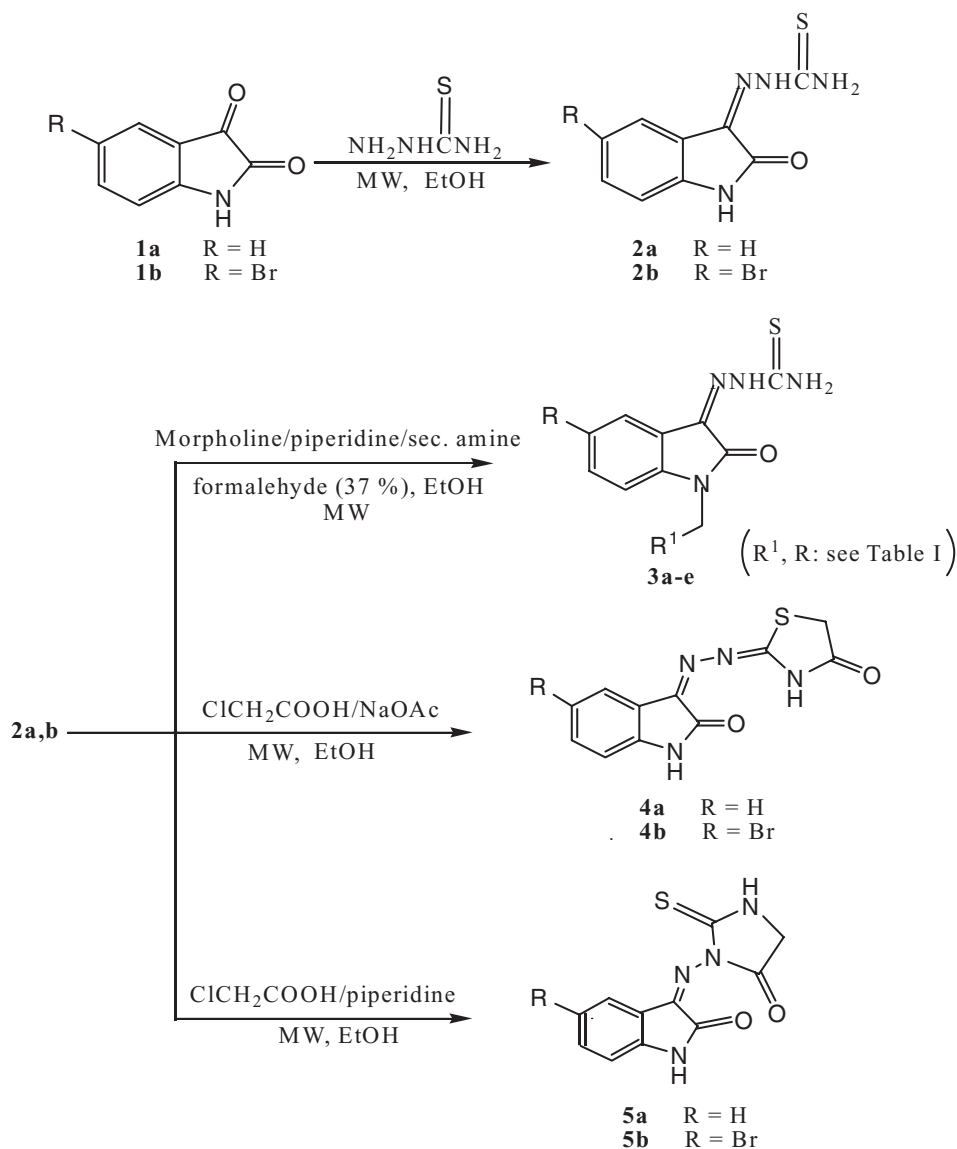
Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were obtained with a JEOL AL 300 FTNMR spectrometer, and the chemical shifts are given in ppm using TMS as internal reference. All commercially available chemicals were purchased from Merck and Aldrich.

**Table I** Yields and physical data of compounds **2–5**

Compound	R	R <sup>1</sup>	Formula	MW <sup>a</sup> Time (min)	Yield <sup>b</sup> (%)	Mp (°C)
<b>2a</b>	H	—	C <sub>9</sub> H <sub>8</sub> N <sub>4</sub> SO	4	75	240
<b>2b</b>	Br	—	C <sub>9</sub> H <sub>7</sub> N <sub>4</sub> SOBr	4	80	255
<b>3a</b>	H	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>14</sub> H <sub>19</sub> N <sub>5</sub> OS	4	87	130
<b>3b</b>	H		C <sub>15</sub> H <sub>19</sub> N <sub>5</sub> OS	5	85	180
<b>3c</b>	H		C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> S	5	90	210
<b>3d</b>	Br		C <sub>15</sub> H <sub>18</sub> N <sub>5</sub> OSBr	4	84	215
<b>3e</b>	Br		C <sub>14</sub> H <sub>16</sub> N <sub>5</sub> O <sub>2</sub> SBr	5	82	230
<b>4a</b>	H	—	C <sub>11</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> S	9	90	210
<b>4b</b>	Br	—	C <sub>11</sub> H <sub>7</sub> N <sub>4</sub> O <sub>2</sub> SBr	7	85	245
<b>5a</b>	H	—	C <sub>11</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> S	8	92	225
<b>5b</b>	Br	—	C <sub>11</sub> H <sub>7</sub> N <sub>4</sub> O <sub>2</sub> SBr	7	80	260

<sup>a</sup>Irradiation at 160 W.

<sup>b</sup>Isolated yield.



Scheme 1

### Synthesis of Compounds 2: General Procedure

Isatin/5-bromoisatin **1a/1b** (0.01 mol) and thiosemicarbazide (0.011 mol) were introduced into a 100 mL conical flask containing ethanol (15 mL) and a few drops of glacial acetic acid. The reaction mixture was irradiated in an LG domestic microwave oven for 4 min at 160 W and was subsequently allowed to cool at room temperature. The mixture was filtered and washed with water (10 mL), and the resulting precipitate was recrystallized from ethanol (2 mL) to afford compounds **2**.

### Synthesis of Compounds 3: General Procedure

To a stirred suspension of isatin/5-bromo isatin **2a/2b** (2 mmol) and formaldehyde solution (37%, 0.5 mL) in absolute ethanol (10 mL) in a 100 mL conical flask, a mixture of morpholine/piperidine/*N,N*-diethylamine (2 mmol) was added dropwise. The reaction mixture was then introduced into the microwave oven and was irradiated for 4–5 min at 160 W. The course of the reaction was monitored by TLC. The resulting mixture was allowed to stand overnight, and the resulting solid product was filtered and washed with petroleum ether (10 mL) to furnish pure compounds **3a–e**.

### Synthesis of Compounds 4: General Procedure

A mixture of **2a/2b** (0.01 mol), chloroacetic acid (0.015 mol), and anhydrous sodium acetate (0.15 g) was placed in a 100 mL conical flask containing ethanol (10 mL) and was irradiated in the microwave oven at 160 W for 7–9 min. After the reaction was complete (TLC), the mixture was allowed to cool to room temperature. The resulting solid was filtered, washed with water (10 mL), and recrystallized from ethanol (2 mL) to provide compounds **4a,b**.

### Synthesis of Compounds 5: General Procedure

A mixture of **2a/2b** (0.01 mol), chloroacetic acid (0.01 mol), and piperidine (1.5 mL) in a 100 mL conical flask containing ethanol (10 mL) was introduced into the microwave oven. The reaction mixture was initially irradiated for 30 sec at 160 W. After a break for 1 min and cooling to room temperature, it was again irradiated for 7–8 min. The solid product obtained was filtered, washed with water (10 mL), and recrystallized from ethanol (2 mL) to afford compounds **5a,b**.

### Data

**1*H*-Indole-2,3-dione-3-thiosemicarbazone (2a).** Mp: 240°C (lit.<sup>21</sup> 247–249°C); IR (KBr):  $\nu = 3425, 3238, 1682, 1611, 1130\text{ cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta = 12.45$  (s, 1H), 11.18 (s, 1H), 9.02 (s, 1H), 8.67 (s, 1H), 7.65 (dd,  $J = 1.6\text{ Hz}$ ,  $J = 7.9\text{ Hz}$ , 1H), 7.35 (t,  $J = 8.4\text{ Hz}$ , 1H), 7.08 (t,  $J = 8.4\text{ Hz}$ , 1H), 6.91 (d,  $J = 7.8\text{ Hz}$ , 1H), <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta = 108, 112.2, 116, 120, 129, 137, 155, 162$  (C=O/C=S), 176 (C=O/C=S).

**5-Bromo-1*H*-indole-2,3-dione-3-thiosemicarbazone (2b).** Mp: 255°C; IR (KBr):  $\nu = 3430, 3230, 1690, 1133\text{ cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta = 12.47$  (s, 1H), 11.17 (s, 1H), 9.02 (s, 1H), 8.68 (s, 1H), 7.74 (d,  $J = 7.4\text{ Hz}$ , 1H), 7.41 (t,  $J = 8.5\text{ Hz}$ , 1H), 7.12 (m, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta = 108.3, 112.5, 117.6, 121.9, 131.4, 140.0, 156.5, 164$  (C=O/C=S), 175 (C=O/C=S).

***N*<sup>1</sup>-Diethylaminomethyl-indole-2,3-dione-3-thiosemicarbazone (3a).** Mp: 130°C (Lit.<sup>22</sup> 135°C); IR (KBr):  $\nu = 3436, 3240, 1670, 1140\text{ cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta = 12.11$  (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 7.73 (dd,  $J = 1.8\text{ Hz}$ ,  $J = 7.5\text{ Hz}$ , 1H), 7.45 (m, 1H), 7.17 (m, 1H), 7.20 (d,  $J = 8.0\text{ Hz}$ , 1H), 4.52 (s, 2H), 2.65 (q,  $J = 6.8\text{ Hz}$ , 4H), 1.08 (t,  $J = 6.9\text{ Hz}$ , 6H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta = 16.6$  (CH<sub>3</sub>), 39.5 (CH<sub>2</sub>), 61.7 (N-CH<sub>2</sub>-N), 108, 112, 118.5, 121.8, 132, 140, 157, 163 (C=O/C=S), 175 (C=O/C=S).

***N*<sup>1</sup>-Piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3b).** Mp: 180°C (lit.<sup>22</sup> 177–178°C); IR (KBr):  $\nu = 3427, 2925, 1700, 1162\text{ cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta = 12.36$  (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 7.71 (dd,  $J = 1.6\text{ Hz}$ ,  $J = 7.8\text{ Hz}$ , 1H), 7.41 (m, 1H), 7.26 (d,  $J = 7.8\text{ Hz}$ , 1H), 7.17 (m, 1H), 4.47 (s, 2H), 2.54 (t,  $J = 4.8\text{ Hz}$ ,

4H), 1.46 (m, 4H), 1.33 (m, 2H),  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 24.2, 25.8, 39.6 ( $\text{CH}_2$ ), 62.5 ( $\text{N-CH}_2\text{-N}$ ), 107.8, 112.5, 117, 121, 130.5, 140, 155, 162 ( $\text{C=O/C=S}$ ), 177 ( $\text{C=O/C=S}$ ).

***N*<sup>1</sup>-Morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3c).**

Mp: 210°C (lit.<sup>22</sup> 215–216°C); IR (KBr):  $\nu$  = 3447, 3206, 2852, 1692, 1149  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.38 (s, 1H), 9.05 (s, 1H), 8.71 (s, 1H), 7.73 (dd,  $J$  = 1.8 Hz,  $J$  = 7.8 Hz, 1H), 7.42 (m, 1H), 7.27 (d,  $J$  = 8.2 Hz, 1H), 7.15 (m, 1H), 4.49 (s, 2H), 3.54 (br s, 4H), 2.58 (br s, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 50.9 ( $\text{CH}_2$ ), 61.8 ( $\text{N-CH}_2\text{-N}$ ), 64.4 ( $\text{CH}_2$ ), 107.7, 112.8, 117.5, 121, 130.3, 140, 158.2, 162 ( $\text{C=O/C=S}$ ), 177.5 ( $\text{C=O/C=S}$ ).

**5-Bromo-*N*<sup>1</sup>-piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3d).** Mp: 215°C; IR (KBr):  $\nu$  = 3447, 2933, 1695, 1112  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.37 (s, 1H), 9.06 (s, 1H), 8.69 (s, 1H), 7.78 (d,  $J$  = 2.4 Hz, 1H), 7.45 (m, 1H), 7.28 (d,  $J$  = 8.2 Hz, 1H), 4.48 (s, 2H), 2.52 (t,  $J$  = 4.5 Hz, 4H), 1.46 (m, 4H), 1.34 (m, 2H),  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 24.5, 25.6, 39.5 ( $\text{CH}_2$ ), 61.2 ( $\text{N-CH}_2\text{-N}$ ), 107.2, 112.5, 118, 121.2, 130.7, 140, 158.7, 163 ( $\text{C=O/C=S}$ ), 177 ( $\text{C=O/C=S}$ ).

**5-Bromo-*N*<sup>1</sup>-morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3e).** Mp: 230°C; IR (KBr):  $\nu$  = 3440, 2925, 1691, 1145  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.39 (s, 1H), 9.05 (s, 1H), 8.68 (s, 1H), 7.80 (d,  $J$  = 2.4, 1H), 7.47 (m, 1H), 7.30 (d,  $J$  = 8.2 Hz, 1H), 4.50 (s, 2H), 3.54 (br s, 4H), 2.56 (br s, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 49.5 ( $\text{CH}_2$ ), 61.6 ( $\text{N-CH}_2\text{-N}$ ), 64.3 ( $\text{CH}_2$ ), 107.6, 112.5, 117.9, 122, 130.7, 140, 159, 163 ( $\text{C=O/C=S}$ ), 176.5 ( $\text{C=O/C=S}$ ).

**2-(Isatin-3-azino)-4-thiazolidinone (4a).** Mp: 210°C; IR (KBr):  $\nu$  = 3260, 1675, 1467, 1129  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.46 (s, 1H), 11.18 (s, 1H), 7.66 (dd,  $J$  = 1.8 Hz,  $J$  = 8.2 Hz, 1H), 7.37 (m, 1H), 7.10 (m, 1H), 6.93 (d,  $J$  = 8.5 Hz, 1H), 3.30 (s, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 41.5, 151 (thiazolidinone), 109, 111.3, 116, 122.8, 129, 142, 155, 165 ( $\text{C=O}$ ), 174 ( $\text{C=O}$ ).

**5-Bromo-2-(isatin-3-azino)-4-thiazolidinone (4b).** Mp: 245°C; IR(KBr):  $\nu$  = 3272, 1690, 1484, 1136  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.45 (s, 1H), 11.19 (s, 1H), 7.74 (d,  $J$  = 2.2 Hz, 1H), 7.41 (m, 1H), 7.13 (m, 1H), 3.29 (s, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 41.5, 151 (thiazolidinone), 109, 110.8, 116, 122.8, 129.8, 142, 155.7, 165 ( $\text{C=O}$ ), 175.2 ( $\text{C=O}$ ).

**3-(Isatin-3-imino)-2-thiohydantoin (5a).** Mp: 225°C; IR(KBr):  $\nu$  = 3269, 1675, 1467, 1127  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.26 (s, 1H), 11.29 (s, 1H), 7.80 (dd,  $J$  = 1.6 Hz,  $J$  = 8.5 Hz, 1H), 7.47 (m, 1H), 6.86 (m, 1H), 6.77 (d,  $J$  = 8.7 Hz, 1H), 3.32 (s, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 57.5 (thiohydantoin), 108, 112, 116.5, 122.7, 126, 143, 154, 163 ( $\text{C=O/C=S}$ ), 171.5 ( $\text{C=O/C=S}$ ), 179 ( $\text{C=O/C=S}$ ).

**5-Bromo-3-(isatin-3-imino)-2-thiohydantoin (5b).** Mp: 260°C; IR(KBr):  $\nu$  = 3274, 1693, 1485, 1137;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 12.27 (s, 1H), 11.28 (s, 1H), 7.87 (d,  $J$  = 2.2 Hz, 1H), 7.51 (m, 1H), 6.89 (m, 1H), 3.34 (s, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ): 57.3 (thiohydantoin), 107.8, 112, 117, 122.5, 126.2, 143, 154.2, 162 ( $\text{C=O/C=S}$ ), 172 ( $\text{C=O/C=S}$ ), 180 ( $\text{C=O/C=S}$ ).

## REFERENCES

- (a) S. Caddick and R. Fitzmaurice, *Tetrahedron*, **65**, 3325 (2009); (b) C. O. Kappe, *Angew. Chem. Int. Ed. Engl.*, **43**, 6250 (2004); (c) D. Dallinger and C. O. Kappe, *Chem. Rev.*, **107**, 2563 (2007); (d) P. Lidström, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, **57**, 9225 (2001).
- (a) F. D. Poop, *Adv. Heterocycl. Chem.*, **18**, 1 (1975); (b) J. F. M. da Silva, S. J. Garden, and A. C. Pinto, *J. Braz. Chem. Soc.*, **12**, 273 (2001).

3. R. W. Daisley and V. K. Shah, *J. Pharm. Sci.*, **73**, 407 (1984).
4. B. Piscopo, M. V. Diumo, R. Godliardi, M. Cucciniello, and G. Veneruso, *Bol. Soc. Ital. Biol. Super.*, **63**, 827 (1987).
5. I. Chiyanzu, C. Clarkson, P. J. Smith, J. Lehman, J. Gut, P. J. Rosenthal, and K. Chibale, *Bioorg. Med. Chem.*, **13**, 3249 (2005).
6. T. R. Bal, B. Anand, P. Yogeswari, and D. Sriram, *Bioorg. Med. Chem. Lett.*, **15**, 4451 (2005).
7. K. S. Sessaiah, S. Muniyandy, and R. Atrnkuru, *Eur. J. Med. Chem.*, **36**, 615 (2001).
8. D. Sriram, P. Yogeeswari, and G. Gopal, *Eur. J. Med. Chem.*, **40**, 1373 (2005).
9. N. Karali, A. Gürsoy, F. Kandemirli, N. Shvets, F. B. Kaynak, S. Ozbey, V. Kovalishyn, and A. Dimoglo, *Bioorg. Med. Chem.*, **15**, 5888 (2007).
10. S. N. Pandeya, D. Sriram, E. Declercq, and G. Nath, *Eur. J. Pharm. Sci.*, **9**, 25 (1999).
11. M. C. Pirrung, S. V. Panasare, K. Das Sarma, K. A. Keith, and E. R. Kern, *J. Med. Chem.*, **48**, 3045 (2005).
12. R. J. Meis and R. C. Condit, *Virology*, **182**, 442 (1991).
13. F. Lecaille, J. Kaleta, and D. Bromme, *Chem. Rev.*, **102**, 4459 (2002).
14. X. Du, C. Guo, E. Hansell, P. S. Doyle, C. R. Caffery, T. P. Holler, J. H. McKerrow, and F. E. Cohen, *J. Med. Chem.*, **45**, 2695 (2002).
15. C. D. Wang, X. Z. Shi, and Y. H. Feng, *Synth. Commun.*, **29**, 3057 (1999).
16. W. J. Brouillette, V. P. Jestkov, M. L. Brown, M. S. Akhtar, D. M. Delorey, and G. B. Brown, *J. Med. Chem.*, **37**, 3289 (1994).
17. J. J. Scicinski, M. D. Barker, P. J. Murray, and E. M. Jarvie, *Bioorg. Med. Chem. Lett.*, **8**, 3609 (1998).
18. J. E. Tompkins, *J. Med. Chem.*, **29**, 855 (1986).
19. (a) A. Rao, J. Balzarini, A. Carbone, A. Chimirri, E. Declercq, A. M. Monforte, P. Monforte, C. Pannecouque, and M. Zappala, *Il Farmaco*, **59**, 33 (2004); (b) A. Rao, J. Balzarini, A. Carbone, A. Chimirri, E. Declercq, A. M. Monforte, P. Monforte, C. Pannecouque, and M. Zappala, *Antiviral Res.*, **63**, 79 (2004).
20. A. Verma and S. K. Saraf, *Eur. J. Med. Chem.* **43**, 897 (2008).
21. J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *J. Am. Chem. Soc.*, **73**, 906 (1951).
22. R. S. Verma and L. W. Nobles, *J. Med. Chem.*, **10**, 972 (1967).