

RESEARCH ARTICLE

Open Access

# Microwave irradiation: synthesis and characterization of $\alpha$ -ketoamide and bis ( $\alpha$ -ketoamide) derivatives via the ring opening of *N*-acetylisatin

Ayman El-Faham<sup>1,2\*</sup>, Sherine N Khattab<sup>2</sup>, Hazem A Ghabbour<sup>3</sup>, Hoong-Kun Fun<sup>3</sup> and M Rafiq H.Siddiqui<sup>1\*</sup>

## Abstract

**Background:** The carbonyl group at position 2 of *N*-acetylisatin behaves as an amide which is more susceptible to nucleophilic attack via ring-opening in the presence of nucleophiles. Because of this behavior, in the present work we describe the microwave synthesis of a series of  $\alpha$ -ketoamide and bis- ( $\alpha$ -ketoamide) derivatives via the facile ring-opening of *N*-acylisatin with different amines and diamines. The microwave irradiation afforded the product in less reaction time, higher yield and purity. Reaction of *N*-acylisatin with methanol under microwave irradiation afforded the  $\alpha$ -phenylglyoxyl methyl ester derivatives with excellent yields and purities. Aminolysis of the ester derivatives with piperidine and morpholine afforded the same  $\alpha$ -ketoamide derivatives obtained from direct aminolysis of *N*-acylisatin. The structures of the synthesized compounds were confirmed by FT-IR, NMR, X-ray and elemental analysis.

**Results:** Reaction of *N*-acetylisatin and *N*-propionylsatin with different amines and diamines afforded a series of  $\alpha$ -ketoamide and bis- ( $\alpha$ -ketoamide) derivatives respectively via the ring opening of *N*-acylisatins. The reaction was performed under conventional condition as well as microwave irradiation. The microwave irradiation afforded the product in less reaction time, higher yield and purity. Reaction of *N*-acylisatin with methanol under microwave irradiation afforded the  $\alpha$ -phenylglyoxyl methyl ester derivatives in excellent yields and purities as observed from their spectral data. A plausible mechanism involves nucleophilic attack by methanol at C2 carbonyl carbon of *N*-acetylisatin and subsequent ring opening to generate the  $\alpha$ -ketoester. Aminolysis of  $\alpha$ -ketoester with amine afforded the same  $\alpha$ -ketoamide which is obtained by direct aminolysis of *N*-acylisatin. The IR, NMR spectra, microanalyses, and single crystal X-ray diffraction confirmed the structures of the synthesized compounds.

**Conclusions:** In conclusion, we have demonstrated that microwave irradiation could be employed efficiently for the synthesis of biologically important  $\alpha$ -ketoamide and bis- ( $\alpha$ -ketoamide) derivatives. The microwave irradiation has more advantageous over the classical method with regard to reaction time, solvent quantity, and product yield. Reaction of *N*-acylisatin with methanol under microwave irradiation afforded the  $\alpha$ -phenylglyoxyl methyl ester derivatives with excellent yields and purities. Aminolysis of the methyl ester derivatives with amine under microwave irradiation afford the same  $\alpha$ -ketoamide derivatives as obtained from direct aminolysis of *N*-acylisatins.

**Keywords:** *N*-acetylisatin, *N*-propionylsatin, Microwave irradiation,  $\alpha$ -ketoamide, bis-  $\alpha$ -ketoamide, X-ray crystallography

\* Correspondence: aymanel\_faham@hotmail.com; rafiqs@ksu.edu.sa

<sup>1</sup>Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, 11451 Riyadh, (Kingdom of Saudi Arabia)

<sup>2</sup>Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Ibrahimia 21321 Alexandria, Egypt

Full list of author information is available at the end of the article

## Background

Microwave irradiation (MW) has emerged as a powerful technique offering simple, clean, fast, efficient, and economical method for the synthesis of a large number of biologically active molecules [1-6]. The application of microwave irradiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology [7-14].

The carbonyl group at position 2 of *N*-acetylisatin behaves as an amide carbonyl group which is opposed to the conventional amide carbonyl functionality in isatin [15]. Because of this behavior, *N*-acetylisatin is more susceptible to nucleophilic attack via ring-opening in the presence of nucleophiles, such as amines and alcohols. This ring-opening reaction led to numerous synthetic methods for preparation of  $\alpha$ -ketoamides [16-22], which are of interest in organic and medicinal chemistry [23-27].

In continuation of our earlier work [11,12], we present herein the reaction of *N*-acetyl- and *N*-propionylisatin in methanol with different amines and diamines under microwave irradiation to afford  $\alpha$ -ketoester, series of  $\alpha$ -ketoamide and *bis*-( $\alpha$ -ketoamide) derivatives in excellent yields and purities.

## Results and discussion

Isatin and its derivatives undergo nucleophilic attack at the carbonyl group at position 2 and/or 3. The chemoselectivity of these reactions depends on the nature of the substituent attached to the isatin nucleus, on the nature of the nucleophiles, and the nature of the group attached to the nitrogen atom of the isatin nucleus [15]. *N*-acetylisatin (**1**) undergoes ring-opening reaction with primary amines and alcohols as reported in the literature (Scheme 1) [28].

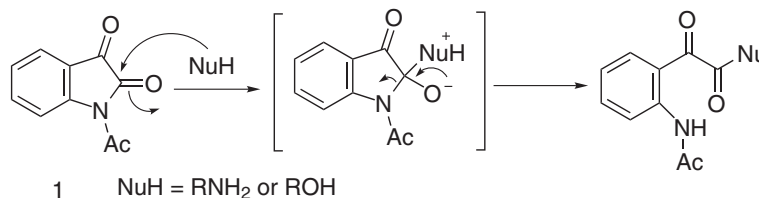
*N*-Acetylisatin (**1**) and *N*-propionylisatin (**2**) were initially prepared by reaction of isatin with acetic anhydride or propanoic anhydride respectively (Scheme 2), using the same reported conventional conditions [29]. Compound **1** and **2** were also prepared by microwave irradiation for 10 min at 100°C/400 W using a multimode reactor (Synthos 3000 Aton Paar, GmbH, 1400 W maximum magnetron) (Scheme 2). The microwave irradiation afforded the product in less reaction time, higher yield and purity than conventional heating.

*N*-Acetylisatin, **1** and *N*-propionylisatin, **2** were reacted with different secondary amines **3a-c** at room temperature in acetonitrile as a solvent to afford  $\alpha$ -ketoamide **4a-c** and **5a-c** in yield 64-72% (Scheme 3). The microwave irradiation of **1** and **2** with different amines **3a-c** afforded the final products **4a-c** and **5a-c** in higher yields and purities than conventional method (Experimental section). The structures of the prepared compounds were confirmed by IR, NMR ( $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ ) and elemental analysis.

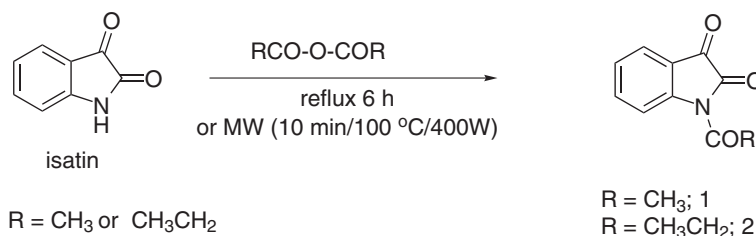
As prototype the IR spectrum of **4a** showed four characteristic peaks at 3399, 1691, 1630, 1605  $\text{cm}^{-1}$ , corresponding to the NH,  $\alpha$ -ketoamide (COCONH) and two CONH, respectively. The  $^1\text{H-NMR}$  of **4a** agreed well with the structure, showing resonance peaks located at  $\delta$  1.55 (m, 2H,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ , piperidine moiety), 1.70 (m, 4H,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ , piperidine moiety), 2.25 (s, 3H,  $\text{COCH}_3$ ), 3.30 and 3.69 (two m, 4H,  $\text{CH}_2\text{-N-CH}_2$ , piperidine moiety), 7.12 (t, 1H, ArH), 7.65 (m, 2H, ArH), 8.88 (d, 1H, ArH), 11.30 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable). The  $^{13}\text{C-NMR}$  of **4a** also confirmed the structure, showing the characteristic signals at  $\delta$  164.5, 169.6 and 196.3 ppm, related to the two carbonyl of the amide group and one related to the  $\alpha$ -ketoamide group respectively along with the rest of the expected carbon signals of the compound. X-Ray single crystal structure determination of compound **4a** and **5a** also confirmed the structure of the products (Figure 1a and b). Crystal data and structure refinement details for compound **4a** and **5a** are shown in Table 1.

Alternatively, the *N*-acylisatin **1** and **2** were dissolved in dry methanol and then irradiated under microwave irradiation for 3–5 min followed by cooling to afford the products **9a** and **9b** in yield 95% and 91%, respectively (Scheme 4). A plausible mechanism involves nucleophilic attack by methanol at C2 carbonyl carbon of *N*-acetylisatin and subsequent ring opening to generate the  $\alpha$ -keto ester (Scheme 4).

The IR spectrum of **9a** showed three carbonyl groups at 1747 (CO-ester), 1696 ( $\alpha$ -CO), and 1657 (CONH)  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum for **9a** showed singlet peaks at  $\delta$  2.25 and 3.99 ppm related to ( $\text{NHCOCH}_3$ ) and ( $\text{COOCH}_3$ ) respectively. The  $^{13}\text{C-NMR}$  of **9a** showed a characteristic peaks for CO-ester and  $\alpha$ -CO- at  $\delta$  169.6 and 190.3 ppm respectively.



**Scheme 1** General mechanism for the reaction of *N*-acylisatin with amine or alcohol.



**Scheme 2** Synthesis of *N*-acylisatin.

The X-ray crystallographic structure for **9a** (Figure 2, Table 2) also confirmed its structure. Crystal data for compound **9a** are shown in Table 2. In the crystal, the molecules are linked via intermolecular N—H—O and C—H—O hydrogen bonds.

Reaction of  $\alpha$ -phenylglyoxyl methyl ester derivatives **9a** and **9b** with piperidine and morpholine under the conventional heating (2 h) and microwave irradiation (2–5 min/80°C/200 W) afforded the same product **4a-b** and **5a-b**, respectively as obtained from the direct aminolysis of *N*-acylisatin **1** and **2** (Scheme 4).

Reaction of *N*-acetylisatin, **1** and *N*-propionylisatin, **2** with different diamines **6a-e** in ratio (2:1) at room temperature for 12 h in acetonitrile as solvent afforded *bis*-( $\alpha$ -ketoamide) **7a-e**, **8a** and **8e** in yields of 68-73% (Scheme 5). The microwave irradiation of **1** and **2** with diamines afforded the products **7a-e**, **8a** and **8e** in higher yield and purity (Experimental section). The structures of the prepared compounds were confirmed by IR, NMR (<sup>1</sup>H-NMR and <sup>13</sup>C-NMR) and elemental analysis

## Experimental section

### Materials and methods

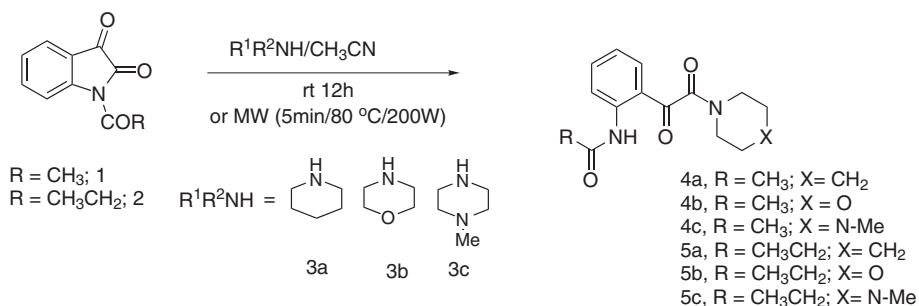
The solvents used were of HPLC reagent grade. Melting points were determined with a Mel-Temp apparatus. Fourier transform infrared spectroscopy (FT-IR) spectra were recorded on Nicolet 560. Nuclear magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra) were recorded on a JOEL 400 MHz spectrometer with chemical shift values reported in  $\delta$  units (ppm) relative to an internal standard.

X-Ray data collection was carried out on Bruker SMART APEX II CCD diffractometer, cell refinement: SAINT; data reduction: SAINT; program used to solve structure: SHELXS; program used to refine structure: SHELXL; molecular graphics: SHELXTL; software used to prepare material for publication: SHELXTL [30] and PLATON [31]. The microwave irradiation employed a multimode reactor (Synthos 3000, Aton Paar GmbH, and 1400 W maximum magnetron). Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values found were within  $\pm 0.3\%$  of the theoretical values. Follow-up of the reactions and checks of the purity of the compounds was done by TLC on silica gel-protected aluminum sheets (Type 60 GF254, Merck). The compounds were named using Chem. Draw Ultra version 11, Cambridge soft Corporation.

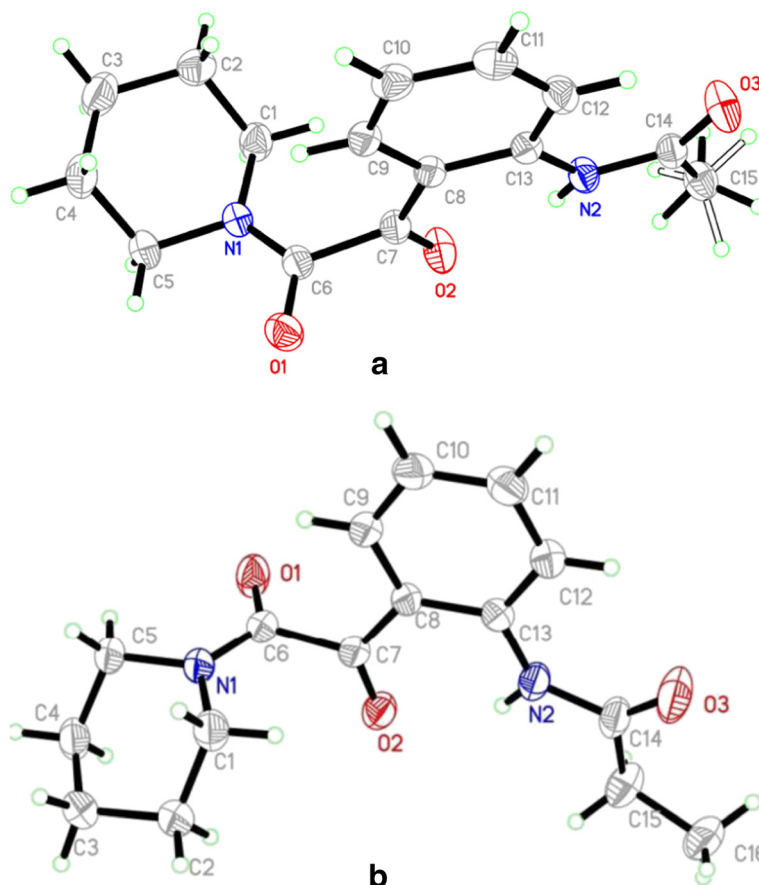
### General method for synthesis of $\alpha$ -ketoamide and *bis*-( $\alpha$ -ketoamide) derivatives

#### Method A (Conventional Procedure)

To a solution of *N*-acetylisatin **1** or *N*-propionylisatin **2** (10 mmol) in acetonitrile (20 mL), secondary amine **3a-c** or diamine **6a-e** in ratio (1:1 and 2:1, respectively) was added at room temperature. The reaction mixture was stirred at room temperature for 12 h. On the next day, the solvent was removed under vacuum and the crude product was recrystallized from dichloromethane and hexane (1:2). In the case of diamine, the precipitate was filtered, washed with acetonitrile (5 mL), and dried under vacuum to afford the pure product.



**Scheme 3** Reaction of *N*-acylisatin with secondary amines.



**Figure 1** ORTEP representation of the crystal structure of **4a** and **5a**. (a) Ortep of N-[2-(2-oxo-2-(piperidin-1-yl)acetyl)phenyl]acetamide **4a** CCDC 943007. (b) Ortep of N-[2-(2-oxo-2-(piperidin-1-yl)acetyl)phenyl]propionamide **5a** CCDC 945756.

#### Method B (Microwave-Irradiation)

The reaction was performed using a multimode reactor (Synthos 3000 Aton Paar, GmbH, 1400 W maximum magnetron). The initial step was conducted with 4-Teflon vessels rotor (MF 100) that allows the reactions to be processed 4 at a time under the same conditions. In each vessel *N*-acylisatin mixed with different amine or diamine in small amount of acetonitrile (2–5 mL). The individual vessels were purged with nitrogen gas for 2 min and then placed in the corresponding rotor. The vessels were heated for 3 min at 80°C and held at the same temperature for a further 2 min at 200 W. Cooling was accomplished by a fan (5 min); the final product was precipitated after cooling, filtered, dried under vacuum, and then recrystallized from dichloromethane-hexane (1:2).

#### N-[2-(2-Oxo-2-(piperidin-1-yl)acetyl)phenyl]acetamide **4a** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 1)

Light brown crystals; mp 132–133°C; yield (65% method A, Lit. [17] mp 130–132 °C); (91% method B); IR (KBr, cm<sup>-1</sup>): 3399 (NH), 1691 (α-COCON), 1630 (CO-amide),

1605 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 1.55 (m, 2H, CH<sub>2</sub>), 1.70 (m, 4H, 2CH<sub>2</sub>), 2.25 (s, 3H, COCH<sub>3</sub>), 3.30 (m, 2H, CH<sub>2</sub>), 3.69 (m, 2H, CH<sub>2</sub>), 7.12 (t, *J* = 8.08 Hz, 1H, ArH), 7.65 (m, 2H, ArH), 8.88 (d, *J* = 8.80 Hz, 1H, ArH), 11.30 (s, 1H, NH, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 24.3, 25.5, 25.7, 26.2, 42.3, 47.2, 117.9, 120.7, 122.8, 133.6, 136.9, 142.5, 164.5 (CO-amide), 169.6 (CO-amide), 196.2 (α-COCON). Anal. Calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.56; H, 6.67; N, 10.33.

#### N-[2-(2-Morpholino-2-oxoacetyl)phenyl]acetamide **4b** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 1)

Light brown crystals; mp 111–113°C; yield (69% method A); (93% method B); IR (KBr, cm<sup>-1</sup>): 3399 (NH), 1693 (α-COCON), 1635 (CO-amide), 1608 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 2.24 (s, 3H, COCH<sub>3</sub>), 3.34 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.65 (t, *J* = 4.40 Hz, 2H, CH<sub>2</sub>), 3.77 (m, 4H, 2CH<sub>2</sub>), 7.13 (t, *J* = 7.36 Hz, 1H, ArH), 7.67 (m, 2H, ArH), 8.78 (d, *J* = 8.04 Hz, 1H, ArH), 11.21 (s, 1H, NH, D<sub>2</sub>O exchangeable) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 25.7, 41.3,

**Table 1 Crystal data and structure refinement details for compounds 4a and 5a**

	4a	5a
<b>Molecular formula</b>	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>
<b>Formula weight</b>	274.31	288.34
<b>Crystal system</b>	Orthorhombic	Triclinic
<b>Space group</b>	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	<i>P</i> 1
<b>Unit cell dimensions</b>	a = 10.0002 (2) Å b = 11.7485 (2) Å c = 11.9183 (2) Å	a = 5.1016 (2) Å, α = 83.188 (2)° b = 8.8474 (3) Å, β = 81.358 (3)° c = 16.9672 (5) Å, γ = 83.745 (3)°
<b>Volume</b>	1400.25 (4) Å <sup>3</sup>	748.54 (4) Å <sup>3</sup>
<b>Z, Calculated density</b>	1.301 g cm <sup>-3</sup>	1.279 g cm <sup>-3</sup>
<b>F(000)</b>	584	308
<b>Crystal size</b>	0.82 × 0.67 × 0.43 mm	0.43 × 0.25 × 0.23 mm
<b>θ range for data collection</b>	θ <sub>max</sub> = 71.8°, θ <sub>min</sub> = 5.3°	θ <sub>max</sub> = 65.0°, θ <sub>min</sub> = 2.7°
<b>Limiting indices</b>	-12 < =h < =12, -12 < =k < =14, -13 < =l < =14	-4 < =h < =5, -10 < =k < =10, -19 < =l < =19
<b>Reflections collected/unique</b>	9719/2682 [R <sub>int</sub> = 0.021]	8120/ 2453 [R <sub>int</sub> = 0.111]
<b>Completeness</b>	to theta 71.6 = 98.8%	to theta 65.0 = 96.8%
<b>Absorption correction</b>	multi-scan SADABS Bruker 2009	multi-scan SADABS Bruker 2009
<b>Refinement method</b>	Full-matrix least-squares on F <sup>2</sup>	Full-matrix least-squares on F <sup>2</sup>
<b>Goodness-of-fit on F<sup>2</sup></b>	1.03	1.64
<b>CCDC number</b>	943007	945756

46.4, 66.7, 117.8, 120.8, 122.9, 133.53, 137.2, 142.6, 164.6 (CO-amide), 169.6 (CO-amide), 195.4 (α-COCON) ppm. Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.78; H, 5.77; N, 10.31.

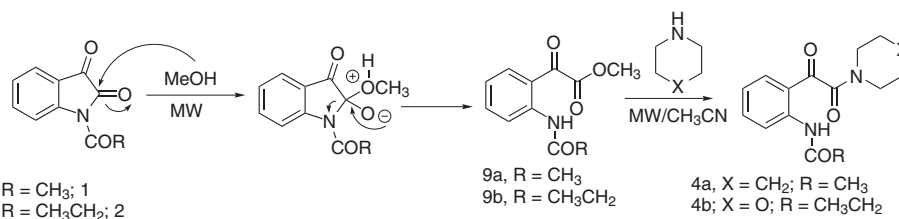
***N*-[2-(2-(4-Methylpiperazin-1-yl)-2-oxoacetyl)phenyl]acetamide 4c** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 1)

Light brown crystals; mp 113-115°C; yield (64% method A); (89% method B); IR (KBr, cm<sup>-1</sup>): 3396 (NH), 1692 (α-CO-CON), 1633 (CO-amide), 1608 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.23 (s, 3H, COCH<sub>3</sub>), 2.30 (s, 3H, N-CH<sub>3</sub>), 2.35 (t, *J* = 5.01 Hz, 2H, CH<sub>2</sub>), 2.49 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.33 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.77 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 7.12 (t, *J* = 7.32 Hz, 1H, ArH), 7.63 (m, 2H, ArH), 8.77 (d, *J* = 8.80 Hz, 1H, ArH), 11.24 (s, 1H, NH, D<sub>2</sub>O exchangeable) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 25.6,

41.3, 46.0, 46.1, 54.5, 54.9, 117.9, 120.7, 122.8, 133.6, 137.1, 142.5, 164.4 (CO-amide), 169.8 (CO-amide), 195.7 (α-COCON). Anal. Calcd for C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.38; H, 6.71; N, 14.69.

***N*-[2-(2-Oxo-2-(piperidin-1-yl)acetyl)phenyl]propionamide 5a** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 2)

Light brown crystals; mp 102-103°C; yield (70% method A); (95% method B); IR (KBr, cm<sup>-1</sup>): 3396 (NH), 1695 (α-CO-CON), 1630 (CO-amide), 1608 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 1.26 (t, *J* = 7.32 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.53 (m, 2H, CH<sub>2</sub>), 1.68 (m, 4H, 2CH<sub>2</sub>), 2.49 (q, *J* = 7.36 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.26 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.68 (m, 2H, CH<sub>2</sub>), 7.12 (t, *J* = 8.08 Hz, 1H, ArH), 7.64 (m, 2H, ArH), 8.81 (d, *J* = 8.80 Hz, 1H, ArH), 11.31 (s, 1H, NH, D<sub>2</sub>O exchangeable) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 9.5, 24.4,



**Scheme 4** Reaction mechanism of *N*-acylisatin with methanol.

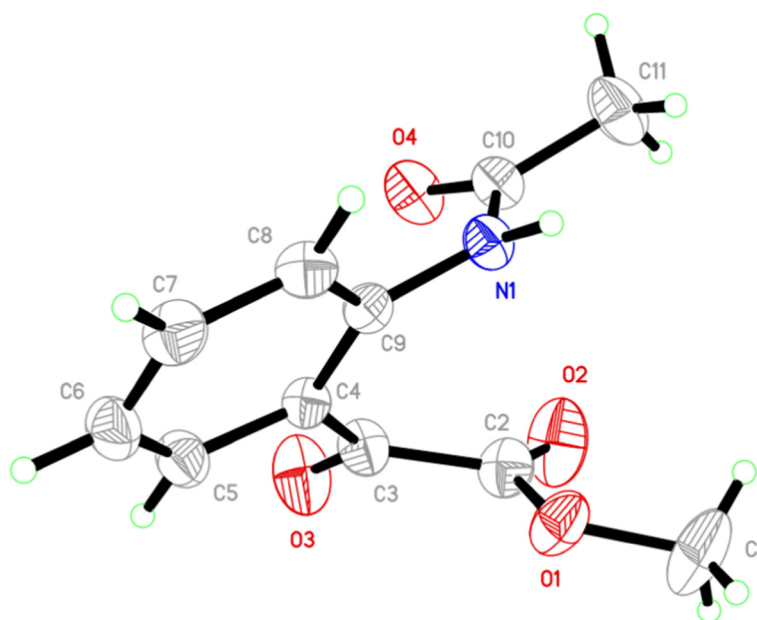


Figure 2 Ortep of methyl 2-(2-acetamidophenyl)-2-oxoacetate 9a CCDC No. 942706.

Table 2 Crystal data and structure refinement details for compound 9a

	9a
Molecular formula	C <sub>11</sub> H <sub>11</sub> NO <sub>4</sub>
Formula weight	221.21
Crystal system	Monoclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>c</i>
Unit cell dimensions	a = 7.3649 (2) Å b = 18.6848 (5) Å c = 9.3738 (3) Å, β = 121.126 (2)°
Volume	1104.23 (5) Å <sup>3</sup>
Z, Calculated density	1.331 g cm <sup>-3</sup>
F(000)	464
Crystal size	0.52 × 0.48 × 0.22 mm
θ range for data collection	θ <sub>max</sub> = 70.1°, θ <sub>min</sub> = 4.7°
Limiting indices	-8 < = h < = 7, -22 < = k < = 22, -9 < = l < = 11
Reflections collected/unique	7581/2018 [R <sub>int</sub> = 0.022]
Completeness	to theta 70.1 = 96.2%
Absorption correction	multi-scan, SADABS Bruker 2009
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Goodness-of-fit on F <sup>2</sup>	1.11
CCDC number	942706

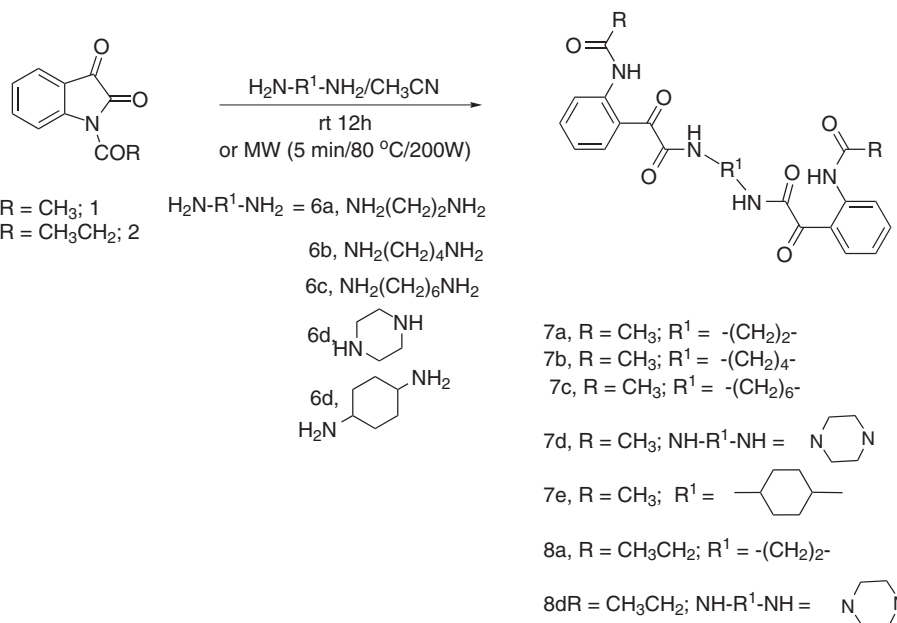
25.4, 25.7, 26.2, 31.8, 42.3, 47.2, 120.7, 118.0, 122.7, 133.5, 136.9, 142.6, 164.5 (CO-amide), 173.4 (CO-amide), 196.2 (α-COCON) ppm. Anal. Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.38; H, 6.81; N, 9.98.

***N*-[2-(2-Morpholino-2-oxoacetyl)phenyl]propionamide 5b** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 2)

Light brown crystals; mp 112-112°C; yield (69% method A); (93% method B); IR (KBr, cm<sup>-1</sup>): 3394 (NH), 1691 (α-CO), 1632 (CO-amide), 1610 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 1.29 (t, *J* = 7.32 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.48 (q, *J* = 7.36 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.36 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.66 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 3.78 (brs, 4H, 2CH<sub>2</sub>), 7.13 (t, *J* = 7.13 Hz, 1H, ArH), 7.67 (m, 2H, ArH), 8.83 (d, *J* = 8.80 Hz, 1H, ArH), 11.24 (s, 1H, NH, D<sub>2</sub>O exchangeable) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 9.5, 31.8, 41.7, 46.4, 66.7, 117.8, 120.9, 122.7, 133.5, 137.2, 142.8, 164.6 (CO-amide), 173.4 (CO-amide), 195.4 (α-COCON) ppm. Anal. Calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.18; H, 6.17; N, 9.89.

***N*-[2-(2-(4-Methylpiperazin-1-yl)-2-oxoacetyl)phenyl]propionamide 5c** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 2)

Light brown crystals; mp 90-92°C; yield (72% method A); (89% method B); IR (KBr, cm<sup>-1</sup>): 3366 (NH), 1710 (α-CO), 1644 (CO-amide), 1581 (CO-amide). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 1.26 (s, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.30 (s, 3H, N-CH<sub>3</sub>), 2.35 (t, *J* = 5.12 Hz, 2H, CH<sub>2</sub>), 2.51 (m, 4H, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>), 3.35 (t, *J* = 4.80 Hz, 2H, CH<sub>2</sub>), 3.77 (t, *J* = 5.16 Hz,



**Scheme 5** Reaction of *N*-acylsatin with diamines.

2H, CH<sub>2</sub>), 7.12 (t, *J* = 8.08 Hz, 1H, ArH), 7.63 (m, 2H, ArH), 8.81 (d, *J* = 8.80 Hz, 1H, ArH), 11.27 (s, 1H, NH, D<sub>2</sub>O exchangeable) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 9.5, 31.8, 41.3, 46.0, 46.4, 54.5, 54.9, 117.9, 120.8, 122.7, 133.6, 137.1, 142.7, 164.5 (CO-amide), 173.4 (CO-amide), 195.7 (α-COCON) ppm. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>: C, 63.35; H, 6.98; N, 13.85; Found: C, 63.21; H, 6.87; N, 14.03.

***N, N'*-(Ethane-1,2-diyl)bis[2-(2-acetamidophenyl)-2-oxoacetamide] 7a** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 3)

White solid; mp 220-221°C (dec.); yield (72% method A); (92% method B); IR (KBr, cm<sup>-1</sup>): 3351 (NH), 1685 (α-CO), 1653 (CO-amide), 1587 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 2.06 (s, 6H, 2 COCH<sub>3</sub>), 3.36 (m, 4H, 2CH<sub>2</sub>), 7.20 (t, *J* = 7.32 Hz, 2H, ArH), 7.65 (t, *J* = 8.08 Hz, 2H, 2 NH), 7.67(d, *J* = 8.08 Hz, 2H, 2ArH), 7.81 (d, *J* = 8.08 Hz, 2H, ArH), 8.84 (d, 2H, ArH), 11.55 (s, 2H, 2NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 24.5, 39.9, 122.1, 124.0, 124.8, 134.4, 138.8, 164.2 (CO-amide), 169.3 (CO-amide), 191.2 (α-COCON) ppm. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>6</sub>: C, 60.27; H, 5.06; N, 12.78; Found: C, 60.38; H, 5.11; N, 12.69.

***N, N'*-(Butane-1,4-diyl)bis[2-(2-acetamidophenyl)-2-oxoacetamide] 7b** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 3)

White solid; mp 205-207°C (dec.); yield (70% method A); (90% method B); IR (KBr, cm<sup>-1</sup>): 3258 (NH), 1698 (α-CO), 1663 (CO-amide), 1602 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 1.55 (m, 4H, 2CH<sub>2</sub>), 2.05 (s, 6H, 2COCH<sub>3</sub>), 3.23 (m, 4H, 2 CH<sub>2</sub>), 7.23 (t, *J* = 8.04 Hz, 2H, ArH), 7.64

(m, 4H, 2NH, 2ArH), 7.89 (d, *J* = 8.08 Hz, 2H, ArH), 8.75 (t, *J* = 5.16 Hz, 2H, ArH), 11.60 (s, 2H, 2NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 24.6, 26.8, 39.6, 121.9, 124.0, 124.2, 132.3, 134.7, 139.2, 164.3 (CO-amide), 169.4 (CO-amide), 192.4 (α-COCON) ppm. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>: C, 61.79; H, 5.62; N, 12.01. Found: C, 61.87; H, 5.71; N, 12.19.

***N, N'*-(Hexane-1,6-diyl)bis[2-(2-acetamidophenyl)-2-oxoacetamide] 7c** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 3)

White solid; mp 176-178°C (dec.); yield (72% method A); (94% method B); IR (KBr, cm<sup>-1</sup>): 3257 (NH), 1698 (α-CO), 1662 (CO-amide), 1608 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 1.33 (m, 4H, 2CH<sub>2</sub>), 1.51 (m, 4H, 2CH<sub>2</sub>), 2.07 (s, 6H, 2 COCH<sub>3</sub>), 3.21 (m, 4H, 2 CH<sub>2</sub>), 7.23 (t, *J* = 7.32 Hz, 2H, ArH), 7.62 (m, 4H, 2NH, 2ArH), 7.91 (d, *J* = 8.08 Hz, 2H, ArH), 8.73 (t, *J* = 5.88 Hz, 2H, ArH), 10.91 (s, 2H, 2NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 24.7, 26.6, 29.6, 39.1, 121.9, 124.0, 124.1, 132.3, 134.7, 139.3, 164.3 (CO-amide), 169.3 (CO-amide), 192.5 (α-COCON) ppm. Anal. Calcd for C<sub>26</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>: C, 63.15; H, 6.11; N, 11.33. Found: C, 63.27; H, 5.98; N, 11.49.

**1, 1'-(Piperazine-1,4-diyl)bis[2-(2-acetamidophenyl)ethane-1,2-dione] 7d** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 4)

White solid; mp 118-120°C (dec.); yield (69% method A); (93% method B); IR (KBr, cm<sup>-1</sup>): 3364 (NH), 1712 (α-CO), 1644 (CO-amide), 1580 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 2.13 (s, 3H, COCH<sub>3</sub>), 2.18 (s, 3H, COCH<sub>3</sub>), 3.41

(m, 2H, CH<sub>2</sub>), 3.55 (m, 2H, CH<sub>2</sub>), 3.64 (m, 2H, CH<sub>2</sub>), 3.77 (m, 2H, CH<sub>2</sub>), 7.29 (m, 2H, ArH), 7.75 (m, 4H, ArH), 8.17 (d, *J* = 8.08 Hz, 1H, ArH), 8.31 (d, *J* = 8.08 Hz, 1H, ArH), 10.73 (s, 1H, NH), 10.83 (s, 1H, NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 25.1, 25.2, 41.1, 41.4, 45.4, 46.0, 121.8, 121.9, 122.1, 124.2, 124.2, 124.4, 133.4, 133.7, 136.5, 136.7, 140.6, 141.0, 164.6 (CO-amide), 164.7 (CO-amide), 169.9 (CO-amide), 193.4 (α-COCON), 193.9 (C = O) ppm. Anal. Calcd for C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>6</sub>: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.31; H, 5.11; N, 12.29.

***N, N'*-(Cyclohexane-1,4-diyl)bis[2-(2-acetamidophenyl)-2-oxoacetamide] 7e** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 4)

Off White solid; mp 249-250°C; yield (68% method A); (89% method B); IR (KBr, cm<sup>-1</sup>): 3269 (NH), 1686 (α-CO), 1645 (CO-amide), 1588 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 1.45 (m, 4H, CH<sub>2</sub>), 1.89 (m, 4H, CH<sub>2</sub>), 2.08 (s, 6H, 2 COCH<sub>3</sub>), 3.67 (m, 2H, CH), 7.26 (t, *J* = 7.36 Hz, 2H, 2ArH), 7.63 (m, 4H, 2NH, 2ArH), 7.97 (d, *J* = 8.08 Hz, 2H, ArH), 8.69 (d, *J* = 8.08 Hz, 2H, 2ArH), 10.64 (s, 2H, 2NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 24.7, 24.8, 31.1, 47.8, 121.8, 121.9, 123.7, 124.1, 132.3, 132.5, 134.7, 135.1, 139.5, 163.8 (CO-amide), 169.4 (CO-amide), 192.7 (α-COCON) ppm. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.28; H, 5.81; N, 11.49.

***N, N'*-(Ethane-1,2-diyl)bis[2-(2-propionamidophenyl)-2-oxoacetamide] 8a** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 5)

White solid; mp 204-206°C (dec.); yield (70% method A); (91% method B); IR (KBr, cm<sup>-1</sup>): 3291 (NH), 1697 (α-CO), 1667 (CO-amide), 1607 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 1.09 (t, *J* = 7.32 Hz, 6H, 2CH<sub>2</sub>CH<sub>3</sub>), 2.37 (q, *J* = 7.33 Hz, 4H, 2CH<sub>2</sub>CH<sub>3</sub>), 3.38 (m, 4H, 2CH<sub>2</sub>), 7.21 (t, *J* = 8.04 Hz, 2H, ArH), 7.62 (t, *J* = 7.32 Hz, 2H, 2NH), 7.69 (d, *J* = 7.32 Hz, 2H, ArH), 7.92 (d, *J* = 8.80 Hz, 2H, ArH), 8.88 (brs, 2H, ArH), 10.60 (s, 2H, 2NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 9.9, 30.4, 39.4, 121.8, 123.8, 124.0, 132.5, 134.7, 139.2, 164.3 (CO-amide), 172.9 (CO-amide), 191.9 (α-COCON) ppm. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>: C, 61.79; H, 5.62; N, 12.01; O, 20.58. Found: C, 62.00; H, 5.51; N, 12.39.

**1, 1'-(Piperazine-1,4-diyl)bis[2-(2-propionamidophenyl)ethane-1,2-dione] 8d** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 5)

White solid; mp 221-223°C; yield (72% method A); (93% method B); IR (KBr, cm<sup>-1</sup>): 3318 (NH), 1701 (α-CO), 1644 (CO-amide), 1581 (CO-amide). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 1.13 (m, 4H, 2CH<sub>2</sub>CH<sub>3</sub>), 2.48 (m, 4H, 2CH<sub>2</sub>CH<sub>3</sub>), 3.40 (m, 2H, CH<sub>2</sub>), 3.55 (m, 2H, CH<sub>2</sub>), 3.64 (m, 2H, CH<sub>2</sub>), 3.78 (m, 2H, CH<sub>2</sub>), 7.29 (m, 2H, ArH), 7.75 (m, 4H, ArH),

8.30 (d, *J* = 8.08 Hz, 1H, ArH), 8.44 (d, *J* = 8.04 Hz, 1H, ArH), 10.80 (s, 1H, NH), 10.90 (s, 1H, NH) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 9.8, 9.8, 30.8, 30.9, 41.1, 41.4, 45.4, 46.0, 120.4, 121.5, 121.7, 124.0, 124.1, 133.7, 134.0, 136.7, 136.9, 141.1, 141.5, 164.7 (CO-amide), 164.7 (CO-amide), 173.3, 193.9 (α-COCON), 194.3 (α-COCON) ppm. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.31; H, 5.81; N, 11.19.

**Synthesis of methyl 2-(2-acetamidophenyl)-2-oxoacetate (9a) and methyl 2-oxo-2-(2-propionamidophenyl)acetate (9b) using microwave irradiation:**

*N*-Acylosatin **1** or **2** (2 mmol) was dissolved in methanol (10 mL) and the reaction was microwave irradiated using a multimode reactor (Synthos 3000 Aton Paar, GmbH, 1400 W maximum magnetron) for 3 min at 80°C and hold at the same temperature for 2 min at 200 W. Cooling was accomplished by a fan (5 min) and the desired product was obtained after cooling with an excellent yield without further recrystallization.

**Methyl 2-(2-acetamidophenyl)-2-oxoacetate 9a** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 6)

The product was obtained as yellow needles from methanol; mp 104-105°C; yield 91%. IR (KBr, cm<sup>-1</sup>): 3220.99 (NH), 1746.58 (CO-ester), 1696.22 (α-CO), 1656.79 (CO-amide). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 2.25 (s, 3H, COCH<sub>3</sub>), 3.98 (s, 3H, COOCH<sub>3</sub>), 7.13 (t, *J* = 7.36 Hz, 1H, Ar), 7.62-7.68 (m, 2H, Ar), 8.78 (d, *J* = 8.08 Hz, 1H, Ar), 11.06 (s, 1H, NH) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 25.6, 53.1, 117.1, 120.8, 122.6, 133.6, 137.3, 142.8, 142.8, 164.0 (CO-amide), 169.6 (CO-ester), 190.3 (α-COCON) ppm. Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub>: C 59.73, H 5.01, N 6.33. Found C 60.00, H 5.18, N 6.44.

**Methyl 2-(2-propionamidophenyl)-2-oxoacetate 9b** (<sup>1</sup>H NMR and <sup>13</sup>C NMR attached as a supporting information; Additional file 7)

The product was obtained as yellow needles from methanol; mp 68-70°C; yield 89%. IR (KBr, cm<sup>-1</sup>): 3220.99 (NH), 1746.58 (CO-ester), 1696.22 (α-CO), 1656.79 (CONH). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, *J* = 7.32 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.48 (q, *J* = 7.32 Hz, 2H, COCH<sub>2</sub>CH<sub>3</sub>), 3.98 (s, 3H, COOCH<sub>3</sub>), 7.13 (t, *J* = 8.04 Hz, 1H, Ar), 7.63-7.68 (m, 2H, Ar), 8.82 (d, *J* = 8.08 Hz, 1H, Ar), 11.10 (s, 1H, NH) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 9.5, 31.8, 53.1, 117.1, 120.8, 122.5, 133.7, 137.3, 142.9, 164.0 (CO-amide), 173.4 (CO-ester), 190.4 (α-COCON) ppm. Anal. Calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub>: C, 61.27; H, 5.57; N, 5.95. Found C 61.05, H 5.71, N 6.04.

**Conclusions**

In conclusion, we have demonstrated that microwave irradiation could be employed efficiently for the synthesis



of biologically important  $\alpha$ -ketoamide and *bis*-( $\alpha$ -ketoamide) derivatives. The microwave irradiation showed more advantageous over the classical method with regard to reaction time, solvent quantity, and product yield in almost every case. Reaction of *N*-acylisatin with methanol under microwave irradiation afforded the  $\alpha$ -phenylglyoxyl methyl ester derivatives with an excellent yield and purity. Aminolysis of phenylglyoxyl ester derivatives with piperidine and morpholine under microwave irradiation afford the same  $\alpha$ -ketoamide derivatives as obtained from direct aminolysis of *N*-acylisatin with amine.

## Additional files

### Additional file 1: $^1\text{H}$ NMR spectra of compound of compound 4a.

$^{13}\text{C}$  NMR spectra of compound of compound 4a.  $^1\text{H}$  NMR spectra of compound of compound 4b.  $^{13}\text{C}$  NMR spectra of compound of compound 4b.  $^1\text{H}$  NMR spectra of compound of compound 4c.  $^{13}\text{C}$  NMR spectra of compound of compound 4c.

### Additional file 2: $^1\text{H}$ NMR spectra of compound of compound 5a.

$^{13}\text{C}$  NMR spectra of compound of compound 5a.  $^1\text{H}$  NMR spectra of compound of compound 5b.  $^{13}\text{C}$  NMR spectra of compound of compound 5b.  $^1\text{H}$  NMR spectra of compound of compound 5c.  $^{13}\text{C}$  NMR spectra of compound of compound 5c.

### Additional file 3: $^1\text{H}$ NMR spectra of compound of compound 7a.

$^{13}\text{C}$  NMR spectra of compound of compound 7a.  $^1\text{H}$  NMR spectra of compound of compound 7b.  $^{13}\text{C}$  NMR spectra of compound of compound 7b.

### Additional file 4: $^1\text{H}$ NMR spectra of compound of compound 7d.

$^{13}\text{C}$  NMR spectra of compound of compound 7d.  $^1\text{H}$  NMR spectra of compound of compound 7e.  $^{13}\text{C}$  NMR spectra of compound of compound 7e.  $^1\text{H}$  NMR spectra of compound of compound 7c.  $^{13}\text{C}$  NMR spectra of compound of compound 7c.

### Additional file 5: $^1\text{H}$ NMR spectra of compound of compound 8a.

$^{13}\text{C}$  NMR spectra of compound of compound 8a.  $^1\text{H}$  NMR spectra of compound of compound 8d.  $^{13}\text{C}$  NMR spectra of compound of compound 8d.

### Additional file 6: $^1\text{H}$ NMR spectra of compound of compound 9a.

$^{13}\text{C}$  NMR spectra of compound of compound 9a.

### Additional file 7: $^1\text{H}$ NMR spectra of compound of compound 9b.

$^{13}\text{C}$  NMR spectra of compound of compound 9b.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

HAG and H-KF carried out X-ray method and the characterization; MRHS, SNK, and AEF carried out the synthesis and designed the proposed methods and analyzed the data statistically together. All authors read and approved the final manuscript.

## Acknowledgement

The authors extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for funding this work through research group project No. RGP-234.

## Author details

<sup>1</sup>Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, 11451 Riyadh, (Kingdom of Saudi Arabia). <sup>2</sup>Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Ibrahimia 21321 Alexandria, Egypt. <sup>3</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box. 2457, 11451 Riyadh, Saudi (Kingdom of Arabia).

Received: 20 September 2013 Accepted: 2 April 2014

Published: 28 April 2014

## References

1. Lidstrom, Tierney J, Wathey B, Westman J: Microwave assisted organic synthesis—a review. *Tetrahedron* 2001, **57**:9225–9283.
2. Perrux L, Loupy AA: A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron* 2001, **57**:9199–9223.
3. Adam D: Microwave Chemistry: Out of the Kitchen. *Nature* 2003, **421**:571–572.
4. Loupy A: Solvent-free microwave organic synthesis as an efficient procedure for green chemistry. *Chimie* 2004, **7**:103–112.
5. Matloobi M, Kappe CO: Microwave Synthesis in High-Throughput Environments. Moving from Automated Sequential to Microtiter Plate Formats. *Chim Oggi* 2007, **25**:26–31.
6. Mallakpour S, Rafiee Z: Application of microwave-assisted reactions in step-growth polymerization: A review. *Iran Polym J* 2008, **17**:907–935.
7. Raval JP, Desai KG, Desai KR: Neat reaction technology for the synthesis of 4-Oxo-thiazolidines derived from 2-SH-benzothiazole and antimicrobial screening of some synthesized 4-thiazolidinones. *J Iranian Chem Soc* 2006, **3**:233–241.
8. Raval JP, Desai JT, Desai CK, Desai KR: A comparative study of microwave assisted and conventional synthesis of 2,3-dihydro-2-aryl-4-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-ylamino]-1,5-benzothiazepines and its antimicrobial activity. *Arkivoc* 2008, **xii**:233–244.
9. Raval JP, Desai KR: A comparative study of microwave-assisted and conventional synthesis of novel 2-(4-diethylamino-2-hydroxyphenyl)-3-substituted-thiazolidin-4-one derivatives. *Lietuvos Mokslu Akademijs* 2009, **20**:101–108.
10. Raval JP, Patel HV, Patel PS, Patel NH, Desai KR: A rapid convenient microwave assisted and conventional synthesis of novel azetidin-2-one derivatives as potent antimicrobial agents. *Asian J Res Chem* 2009, **2**:171–177.
11. Al-Hazimi HM, El-Faham A, Ghazzali M, Al-Farhan K: Microwave irradiation: A facile, scalable and convenient method for synthesis of *N*-phthaloylamino acids. *Arabian J Chem* 2012, **5**:285–289.
12. Ghazzali M, El-Faha A, Abd-Megeed A, Al-Farhan K: Microwave-assisted synthesis, structural elucidation and biological assessment of 2-(2-acetamidophenyl)-2-oxo-*N*-phenyl acetamide and *N*-(2-(2-oxo-2(phenylamino) acetyl)phenyl)propionamide derivatives. *J Mol Str* 2012, **1013**:163–167.
13. Charde M, Shukla A, Bukhariya V, Mehta J, Chakole R: A Review on: A significance of microwave assist technique in green chemistry. *Int J Phytopharm* 2012, **2**:39–50.
14. Ravichandran S, Karthikeyan E: Microwave Synthesis - A Potential Tool for Green Chemistry. *Int J Chem Tech Res* 2011, **3**:466–470.
15. Da Silva JFM, Garden SJ, Pinto AC: The Chemistry of Isatins: a Review from 1975 to 1999. *J Braz Chem Soc* 2001, **12**(3):273–324.
16. Cheah WC, Black DS, Goh WK, Kumar N: Synthesis of anti-bacterial peptidomimetics derived from *N*-acylisatins. *Tetrahedron Lett* 2008, **49**:2965–2968.
17. Obafemi CA, Taiwo FO, Iwalawai EO, Akinpelu DA: Synthesis, Antibacterial And Anti-Inflammatory Activities Of Some 2-Phenylglyoxylic Acid Derivatives. *Int J Life Sci & Pharma Res* 2012, **2**:22–36.
18. Hossain MM, Islam RM, Saha SK, Islam MK: An efficient microwave-assisted synthesis of dihydropyrazinones and bis-benzoylketones. *Tetrahedron Lett* 2010, **51**:1155–1157.
19. Andreani A, Burnelli S, Graniola M, Leoni A, Locatelli A, Morigi R, Rambaldi M, Varoli L, Cremonini MA, Placucci G, Cervellati R, Greco E: New isatin derivatives with antioxidant activity. *Eur J Med Chem* 2010, **45**:1374–1378.
20. Boechar N, Kover WB, Bastos MM, Pinto AC, Maciel LC, Mayer LMU, da Silva FSQ, Sá PM, Mendonça JS, Wardella SMSV, Arruda MSL: *N*-Acyl-3,3-difluoro-2-oxoindoles as versatile intermediates for the preparation of different 2,2-difluorophenylacetic derivatives. *J Braz Chem Soc* 2008, **19**:445–457.
21. Cheah WC, Wood K, Black DSC, Kumar N: Facile ring-opening of *N*-acylisatins for the development of novel peptidomimetics. *Tetrahedron* 2011, **67**:7603–7610.
22. Kidwai M: Green chemistry trends toward sustainability. *Pure Appl Chem* 2006, **78**:1983–1992.
23. Li Z, Ortega-Vilain A-C, Patil GS, Chu D-L, Foreman JE, Eveleth DD, Powers JC: Novel Peptidyl  $\alpha$ -Keto Amide Inhibitors of Calpains and Other Cysteine Proteases. *J Med Chem* 1996, **39**:4089–4098.

24. James DA, Koya K, Li H, Liang G, Xia Z, Ying W, Wu Y, Sun L: **Indole- and indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines.** *Bioorg Med Chem Lett* 2008, **18**:1784–1787.
25. Montalban AG, Boman E, Chang C-D, Conde Ceide S, Dahl R, Dalesandro D, Delaet NGJ, Erb E, Ernst JT, Gibbs A, Kahl J, Kessler L, Lundström J, Miller S, Nakanishi H, Roberts E, Saiah E, Sullivan R, Wang Z, Larson C: **The design and synthesis of novel  $\alpha$ -ketoamide-based p38 MAP kinase inhibitors.** *J Bioorg Med Chem Lett* 2008, **18**:1772–1777.
26. Yu P-F, Chen H, Wang J, He C-X, Cao B, Li M, Yang N, Lei Z-Y, Cheng M-S: **Design, Synthesis and Cytotoxicity of Novel Podophyllotoxin Derivatives.** *Chem Pharm Bull* 2008, **56**:831–834.
27. Victor F, Lamar J, Snyder N, Yip Y, Guo D, Yumibe N, Johnson RB, Wang QM, Glass JI, Chen SH: **P1 and P3 optimization of novel bicycproline P2 bearing tetrapeptidyl  $\alpha$ -ketoamide based HCV protease inhibitors.** *Bioorg Med Chem Lett* 2004, **14**:257–261.
28. Popp FD, Piccirilli M: **The reaction of N-acetylisatin with amines.** *J Heterocycl Chem* 1971, **8**:473–475.
29. Chung YM, Im YJ, Kim JN: **Baylis-Hillman Reaction of Isatin Derivatives: Isatins as a New Entry for the Baylis-Hillman Reaction.** *Bull Korean Chem Soc* 2002, **23**:1651–1653.
30. Sheldrick GM: **A short history of SHELX.** *Acta Crystallogr A* 2008, **64**:112–122.
31. Spek AL: **Structure validation in chemical crystallography.** *Acta Crystallogr D Biol Crystallogr* 2009, **65**:148–155.

doi:10.1186/1752-153X-8-27

**Cite this article as:** El-Faham *et al.*: Microwave irradiation: synthesis and characterization of  $\alpha$ -ketoamide and bis ( $\alpha$ -ketoamide) derivatives via the ring opening of N-acetylisatin. *Chemistry Central Journal* 2014 **8**:27.

Publish with **ChemistryCentral** and every scientist can read your work free of charge

*“Open access provides opportunities to our colleagues in other parts of the globe, by allowing anyone to view the content free of charge.”*

W. Jeffery Hurst, The Hershey Company.

- available free of charge to the entire scientific community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:  
<http://www.chemistrycentral.com/manuscript/>



**ChemistryCentral**