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Research Article

An Efficient and Mild Method for the Synthesis and Hydrazinolysis of *N*-Glyoxylamino Acid Esters

Ayman El-Faham,[1,2] Zainab Al Marhoon,[1] Ahmed Abdel-Megeed,[3,4] and Mohamed Siddiqui[1]

[1] *Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[2] *Chemistry Department, Faculty of Science, Alexandria University, P.O. Box 426, Ibrahimia, Alexandria 12321, Egypt*
[3] *Department of Botany and Microbiology, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[4] *Department of Plant Protection, Faculty of Agriculture, Alexandria University, Saba Basha, Alexandria, Egypt*

Correspondence should be addressed to Ayman El-Faham; aymanel_faham@hotmail.com

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N-Glyoxylamino acid ester derivatives were synthesized via the ring opening of *N*-acetylisatin using moderate conditions. During the hydrazinolysis of *N*-glyoxylamino acid ester derivatives with hydrazine hydrate (80%) in methanol, unexpected reduction of the α-keto group occurred to afford *N*-acylamino acid hydrazide derivatives in good yield (80–90%) (Wolff-Kishner type reaction). All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and elemental microanalysis.

1. Introduction

The glyoxylamides are compounds of widespread interest in organic chemistry and present in many biologically active compounds [1–8]. In parallel with the application of the glyoxylamide in medicinal chemistry, numerous synthetic methods have been described in the literature [9–26]. Other authors have also reported that synthesis of the glyoxylamide fragment could be achieved by the ring opening of *N*-acetylisatin **1** by attacking an amine at C2-carbonyl group of *N*-acetylisatin (Scheme 1) [27–35].

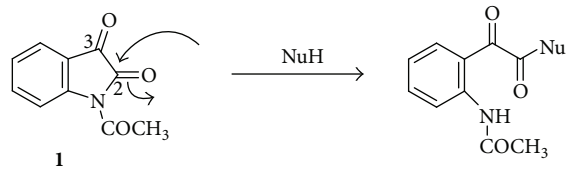
Recently, Cheah et al. [35] reported the synthesis of *N*-glyoxylamide peptide mimics from the reaction of *N*-acetylisatin with L-α-amino esters. The reaction was carried in two-phase solvent system, DCM/H_2O (2 : 1) in the presence of saturated $NaHCO_3$ with yields ranging from 61 to 98%. They claimed that the low yield in some cases is due to the formation of glyoxalic acid derivative (Figure 1).

In the present work, we reported the synthesis of some new *N*-glyoxylamino acid ester using the reported method by Popp and Piccirilli [28] and Obafemi et al. [29] where acetonitrile and K_2CO_3 were used instead of DCM-H_2O/$NaHCO_3$. The products *N*-glyoxylamino acid ester were used as precursors for the synthesis of their hydrazide derivatives with reduction of the α-keto amide group under very mild conditions.

2. Results and Discussion

Ethyl-4-aminobenzoate was selected as a first model to react with *N*-acetylisatin using methanol as a solvent to afford the expected product **2** in yield 87% (Scheme 2). Compound **2** was dissolved in methanol and hydrazine hydrate (80%) was added dropwise at room temperature; the reaction mixture was stirred at the same temperature overnight. The white precipitate formed during the reaction was filtered and dried to afford the product **4** in pure state as indicated from its spectral data. IR for compound **2** showed the carbonyl groups at 1746.09 (CO-ester), 1694.361 (α-CO), 1654.00, and 1603.36 (CONH) cm^{-1}, while the IR spectra of **4** showed only the carbonyl group at 1676.44, 1611.89, and 1563.43 (CONH) cm^{-1} with the disappearance of the α-keto group at 1694 cm^{-1}.

The ^{1}H NMR of **4**, also confirmed the structure, where a singlet peak was observed at δ 4.48 corresponding to



Scheme 1: Formation of glyoxylamide from *N*-acylisatin.

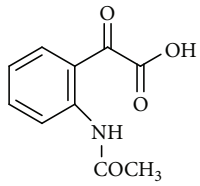


Figure 1: Structure of glycoxalic acid derivative.

the methylene group. The ^{13}C NMR of **4** also confirmed its structure, where the α-keto group at δ 185.61 ppm was not observed but instead a methylene group was observed at δ 87.45 ppm. The data obtained from the IR and NMR spectral analysis proved the suggested mechanism illustrated in Scheme 2. During the hydrazinolysis of **2** with hydrazine hydrate (80%), compound **3** was formed and then undergoes reduction due to the presence of excess of hydrazine [36–39] (Wolff-Kishner type reaction) to afford the product **4** instead of the ketoamide hydrazide derivative **5** (Scheme 2).

In the light of the reaction conditions described in Scheme 2, the same reaction was carried out using methyl-2-aminobenzoate **6**; after removing of the solvent, yellow crystals were formed. The spectral data of the product obtained agreed with the structure of **7** (Scheme 3); where the IR spectra of **7** showed three carbonyl groups corresponding to α-ketoester ($COCOOCH_3$) and amide group ($NHCOCH_3$) at 1746.66, 1695.87, and 1605.65 cm^{-1}, respectively. The ^{1}H NMR confirmed the structure of **7**, where two singlet peak were observed at δ = 2.25 and 3.99 ppm corresponding to the methyl group $NHCOCH_3$ and $COOCH_3$, respectively. The ^{13}C NMR also confirmed the structure of **7**, where two singlet peak were observed at δ = 25.60, 53.06, and 190.32 ppm corresponding to ($NHCOCH_3$), ($COOCH_3$), and (C_6H_4COCO–), respectively, with other peaks related to the rest of carbons skeleton.

The reaction of **1** with methyl-2-aminobenzoate was repeated in acetonitrile instead of methanol, and only about 8–10% yield of **8** was formed even after reflux in acetonitrile for 12 h as observed for the NMR data. These results might be due the steric hindrance of methyl-2-aminobenzoate; *N*-acetylisatin **1** undergoes ring opening in presence of methanol to afford **7** as a major product (Scheme 3).

The reaction of *N*-acetylisatin **1** was extended to react with other amino acid ester hydrochloride **9a–d** [40, 41]. The reaction was performed in CH_3CN and K_2CO_3 at rt to afford the products **10a–d** in 80–92% yield (Scheme 4, Table 1). The products **10a–d** were subject to react with hydrazine hydrate under the same conditioned described in Scheme 3 to afford products **11a–d** in 80–92% yield (Scheme 4, Table 1).

The structures **10a–d** and **11a–d** were confirmed by IR, NMR (^{1}H NMR and ^{13}C NMR), and elemental analysis.

3. Conclusions

The acetonitrile/K_2CO_3 method avoids the formation of the glyoxylic acid formation during the synthesis of *N*-glyoxylamino acid ester from the ring opening of *N*-acetylisatin. The hydrazine hydrate-methanol is an efficient and mild one-pot synthetic method for the preparation of *N*-phenyl acylamino acid hydrazide derivatives from their corresponding *N*-phenylglyoxylamino acid ester derivatives with reduction of the α-keto group (Wolff-Kishner reaction under mild condition) in an excellent yield.

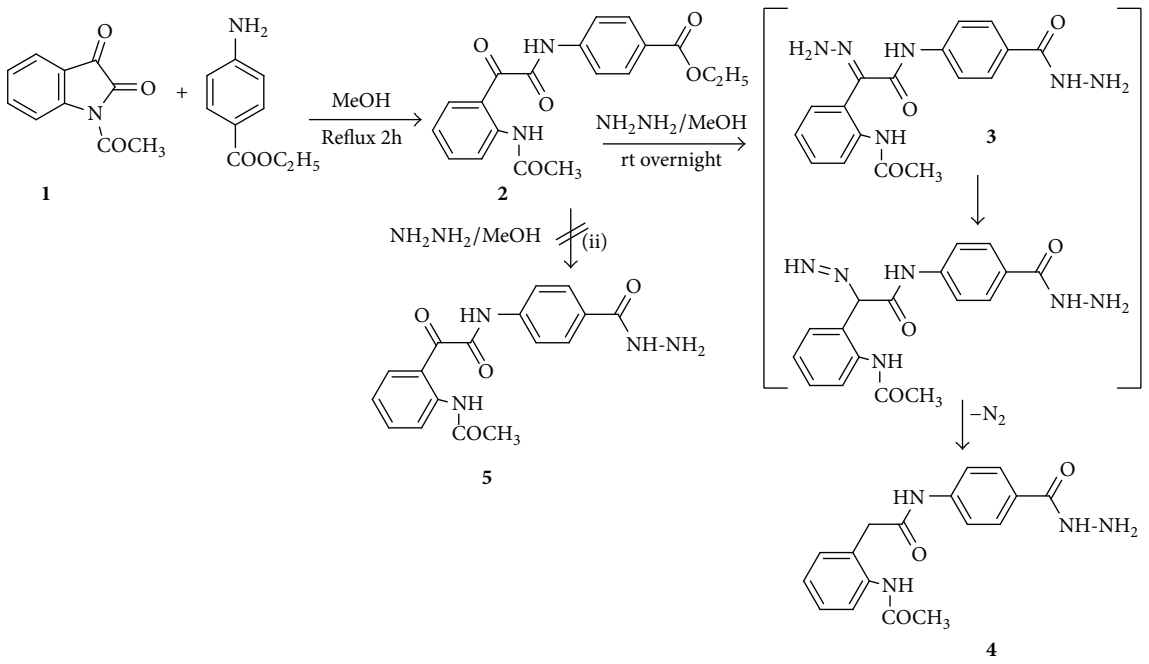
4. Experimental Section

4.1. Materials. The solvents used were of HPLC reagent grade. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Magnetic resonance spectra (^{1}H NMR and ^{13}C NMR spectra) were recorded on a Joel 400 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values found were within ±0.3% of the theoretical values. Followup 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) and the spots were detected by exposure to UV-lamp at λ 254 nm for few seconds. The compounds were named using Chem. Draw Ultra version 11, Cambridge soft Corporation.

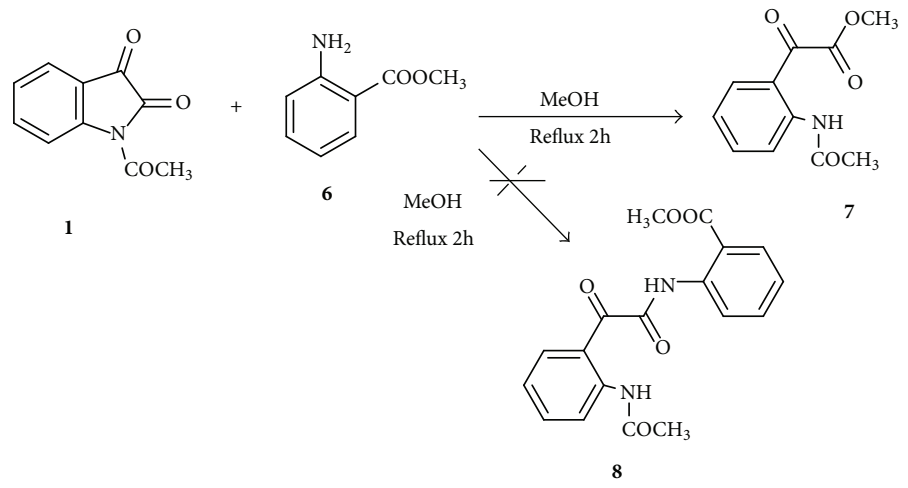
4.2. General Method for the Reaction of N-Acetylisatin with Aminobenzoic Ester Derivatives. To the solution of *N*-acetylisatin **1** (1.89 g, 10 mmol) in methanol (50 mL), which was heated up to 40–50°C, aminobenzoic ester (1.65 g, 10 mmol) was added with intensive stirring. The reaction mixture was refluxed with stirring for 2 h and then cooled down to room temperature. On the next day, the crystalline compound was collected with suction filtration, washed with little cold methanol, and dried under vacuum to afford the pure product.

*4.2.1. Ethyl 4-(2-(2-Acetamidophenyl)-2-oxoacetamido)benzoate (**2**).* The product was obtained as a yellowish white solid from ethanol (mp 78–80°C) in 87% yield. IR (KBr): 3424.75, 3222.27 (NH), 1746.09 (CO-ester), 1694.36 (α-CO), 1654.00, 1603.36 (CONH) cm^{-1}. ^{1}H NMR (d_6-DMSO): δ = 1.26 (t, 3H, CH_3CH_2), 2.03 (s, 3H, $COCH_3$), 4.20 (q, 2H, $COOCH_2CH_3$), 6.57 (d, 2H, Ar), 7.29 (t, 1H, Ar), 7.56 (d, 1H, Ar), 7.63–7.65 (m, 5H, NH, Ar), 10.44 (s, 1H, $NHCOCH_3$) ppm. ^{13}C NMR (d_6-DMSO): δ = 14.92, 23.95, 53.38, 113.25, 116.68, 122.96, 124.80, 126.46, 130.89, 131.57, 134.53, 137.89, 153.86, 163.14, 166.42, 169.65, 185.61 ppm. $C_{19}H_{18}N_2O_5$ (354.36): Calcd. C 64.40, H 5.12, N 7.91; found: C 64.60, H 5.33, N 7.76.

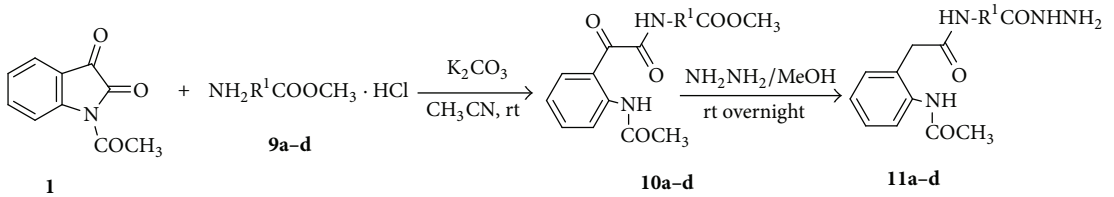
*4.2.2. Methyl 2-(2-Acetamidophenyl)-2-oxoacetate (**7**).* The product was obtained as yellow needles from methanol (mp



Scheme 2: Proposed mechanism for the hydrazinolysis of glyoxylamide ester.



Scheme 3: Reaction of *N*-acetylisatin with methyl-2-aminobenzoate.



$NH_2R^1COOCH_3$ = glycine ethyl ester; **9a**
Methyl-3-aminopropionate; **9b**
Methyl-4-aminobutyrate; **9c**
Methyl-6-aminohexanoate; **9d**

R^1 = CH_2; **11a**
CH_2CH_2; **11b**
$CH_2CH_2CH_2$; **11c**
$CH_2CH_2CH_2CH_2CH_2$; **11d**

Scheme 4: Reaction of *N*-acetylisatin with amino acid ester. HCl and hydrazinolysis.

Table 1: Yield %, Mp (°C) and Elemental Analysis of **10a–d** and **11a–d**.

Cpd no.	Yield (%)	Mp (°C)	Elemental analysis calcd (found)		
			C	H	N
10a	89	108–110	57.53 (57.85)	5.52 (5.81)	9.58 (9.33)
10b	87	90–92	57.53 (57.28)	5.52 (5.81)	9.58 (9.33)
10c	90	100–102	58.82 (59.03)	5.92 (5.81)	9.15 (8.89)
10d	92	92–94	61.07 (61.23)	6.63 (6.79)	8.38 (8.57)
11a	80	198–200	54.54 (54.88)	6.10 (6.43)	21.20 (21.50)
11b	86	204–206	56.10 (55.87)	6.52 (6.81)	20.13 (19.89)
11c	84	195–197	57.52 (57.33)	6.90 (7.11)	19.17 (19.42)
11d	90	186–188	59.98 (60.11)	7.55 (7.67)	17.49 (17.68)

108–110°C) in 92% yield. IR (KBr): 3220.99 (NH), 1746.58 (CO-ester), 1696.22 (α-CO), 1656.79 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.25 (s, 3H, $COCH_3$), 3.99 (s, 3H, $COOCH_3$), 7.14 (t, 1H, Ar), 7.64–7.68 (m, 2H, Ar), 8.78 (d, 1H, Ar), 11.06 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.63, 53.08, 117.03, 120.76, 122.64, 133.63, 137.29, 142.77, 142.77, 163.95, 169.56, 190.34 ppm. $C_{11}H_{11}NO_4$ (221.21): Calcd. C, 59.73; H, 5.01; N, 6.33; found: C 59.95, H 5.31, N 6.44.

*4.3. General Method for the Synthesis of **10a–d**.* To the solution of *N*-acetylisatin **1** (1.89 g, 10 mmol) in acetonitrile (50 mL), amino acid ester hydrochloride [40, 41] (12 mmol) and K_2CO_3 (1.66 g, 12 mmol) were added with intensive stirring. The reaction mixture was stirred at room temperature overnight. On the next day, the reaction mixture was filtered with suction filtration and washed with 10 mL of acetonitrile. The solvent was removed under vacuum to dryness and the crude product was recrystallized from dichloromethane-hexane (1 : 3) to afford the pure product.

*4.3.1. Ethyl 2-(2-(2-Acetamidophenyl)-2-oxoacetamido)acetate (**10a**).* The product was obtained as off-white solid (mp 108–110°C) in 89% yield. IR (KBr): broad peak at 3263.71 for two (NH), 1747.33 (CO-ester), 1673.41 (α-CO), 1645.10, 1579.62 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 1.23 (t, 3H, CH_2CH_3), 2.10 (s, 3H, $COCH_3$), 4.00 (d, 2H, $NHCH_2CO$), 4.15 (q, 2H, $COOCH_2CH_3$), 7.25 (t, 1H, Ar), 7.65 (t, 1H, Ar), 7.76 (d, 1H, Ar), 7.97 (d, 1H, Ar), 9.17 (s, 1H, NH), 10.65 (s, 1H, NH) ppm. ^{13}C NMR (d_6-DMSO): δ = 14.65, 24.73, 40.28, 61.31, 121.31, 123.38, 123.81, 132.58, 135.08, 139.50, 165.00, 169.49, 169.65, 191.95 ppm. $C_{14}H_{16}N_2O_5$ (292.11): Calcd. C 57.53, H 5.52, N 9.58; found C 57.85, H 5.81, N 9.33.

*4.3.2. Methyl 3-(2-(2-Acetamidophenyl)-2-oxoacetamido)propanoate (**10b**).* The product was obtained as off white solid (mp 90–92°C) in 87% yield. IR (KBr): 3287.56, 3124.00 (NH), 1740.76 (CO-ester), 1671.80 (α-CO), 1606.70, 1536.07 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.18 (s, 3H, $COCH_3$), 2.64 (t, 2H, CH_2CH_2CO), 3.67 (q, 2H, $NHCH_2$), 3.70 (s, 3H, $COOCH_3$), 7.09 (t, 1H, Ar), 7.45 (s, 1H, NH), 7.57 (t, 1H, Ar), 8.28 (d, 1H, Ar), 8.62 (d, 1H, Ar), 10.93 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 25.52, 33.49, 35.06, 52.08, 118.57, 120.71, 122.58, 134.37, 136.62, 142.19, 163.05, 169.37, 172.61, 191.90 ppm. $C_{14}H_{16}N_2O_5$ (292.29): Calcd. C 57.53, H 5.52, N 9.58; found: C 57.28, H 5.81, N 9.33.

*4.3.3. Methyl 4-(2-(2-Acetamidophenyl)-2-oxoacetamido)butanoate (**10c**).* The product was obtained as off white solid (mp 100–102°C) in 90% yield. IR (KBr): 3272.48, 3123.79 (NH), 1739.37 (CO-ester), 1667.80 (α-CO), 1606.09, 1532.29 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 1.75 (m, 2H, $CH_2CH_2CH_2$), 2.05 (s, 3H, $COCH_3$), 2.39 (t, 2H, CH_2CH_2CO), 3.21 (q, 2H, $HNCH_2CH_2$), 3.60 (s, 3H, $COOCH_3$), 7.24 (t, 1H, Ar), 7.60–7.63 (m, 2H, Ar), 7.87 (d, 1H, Ar), 8.75 (t, 1H, CH_2NH), 10.60 (1H, s, NHCO). ^{13}C NMR (d_6-DMSO): δ = 24.45, 26.68, 29.56, 31.13, 38.37, 51.87, 122.02, 124.08, 124.79, 131.97, 134.43, 138.76, 164.11, 169.39, 173.63, 191.69 ppm. $C_{15}H_{18}N_2O_5$ (306.31): Calcd. C 58.82, H 5.92, N 9.15; found: C 59.03, H 5.81, N 8.89.

*4.3.4. Methyl 6-(2-(2-Acetamidophenyl)-2-oxoacetamido)hexanoate (**10d**).* The product was obtained as off white solid (mp 92–94°C) in 92% yield. IR (KBr): 3273.64, 3123.48 (NH), 1739.31 (CO-ester), 1667.77 (α-CO), 1606.05, 1532.23 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.37–1.41 (m, 2H, CH_2), 1.59–1.67 (m, 4H, $2CH_2$) 2.17 (s, 3H, $COCH_3$), 2.31 (t, 2H, CH_2), 3.37 (q, 2H, CH_2), 3.64 (s, 3H, $COOCH_3$), 7.03 (t, 1H, $NHCH_2$), 7.09 (t, 1H, Ar), 7.54 (t, 1H, Ar), 8.26 (d, 1H, Ar), 8.57 (d, 1H, Ar), 10.93 (s, 1H, NHCO). ^{13}C NMR ($CDCl_3$): δ = 24.47, 25.50, 26.37, 29.00, 33.83, 39.39, 51.62, 118.76, 120.68, 122.64, 134.40, 136.51, 142.04, 163.17, 169.37, 174.01, 192.39 ppm. $C_{17}H_{22}N_2O_5$ (334.37): Calcd. C 61.07, H 6.63, N 8.38; found: C 61.23, H 6.79, N 8.57.

*4.4. General Method for the Synthesis of (**4** and **11a–d**).* To the solution of glyoxyl derivatives (3 mmol) in methanol (15 mL), 0.7 mL of hydrazine hydrate (80%) was added. The reaction mixture was stirred at room temperature overnight. On the next day, the white precipitate was filtered with suction filtration and washed with cold 5 mL methanol (in case of there is no precipitation formed, the solvent was removed under vacuum and the crude product was washed with ether under stirring) to afford the product in pure state as observed from spectroscopic data.

*4.4.1. 2-(2-Acetamidophenyl)-N-(4-(hydrazinecarbonyl)phenyl)acetamide (**4**).* The product was obtained as a white solid (mp 186–188°C) in 82% yield. IR (KBr): 3420.52, 3338.27, 3340.34, 3209.27 (NH_2 and NH amide), 1676.44, 1611.89 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 2.20 (s, 3H, $COCH_3$), 4.33 (brs, 2H, 2NH), 4.48 (s, 2H, $C_6H_4CH_2CO$), 6.97–6.99 (m, 4H, Ar), 7.08 (s, 1H, NH), 7.17–7.23 (m, 4H, Ar), 9.39 (s, 1H, NH). ^{13}C NMR (d_6-DMSO): δ = 22.38, 87.45, 123.52, 124.08, 125.56, 126.57, 129.45, 142.01, 157.46, 168.93 ppm. $C_{17}H_{18}N_4O_3$ (326.35): Calcd. C 62.57, H 5.56, N 17.17; found C 62.80, H 5.74, N 17.43.

*4.4.2. 2-(2-Acetamidophenyl)-N-(2-hydrazinyl-2-oxoethyl)acetamide (**11a**).* The product was obtained as a white solid (mp 198–200°C) in 80% yield. IR (KBr): broad peak at 3275.61 (NH_2 and NH amide), 1660.66, 1617.14, 1559.58 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 2.20 (s, 3H, $COCH_3$), 3.69–3.79 (m, 2H, CH_2), 4.24 (brs, 2H, 2NH), 4.71 (s, 2H, $C_6H_4CH_2CO$), 6.98 (d, 1H, Ar), 7.16–7.24 (m, 3H, Ar), 8.48 (t, 1H, NH), 9.05 (s, 1H, NH). ^{13}C NMR (d_6-DMSO): δ = 22.33, 41.59, 87.22, 123.68, 124.11, 125.49, 126.63, 129.43, 141.95, 157.40, 168.73, 170.72 ppm. $C_{12}H_{16}N_4O_3$ (264.28): Calcd. C 54.54, H 6.10, N 21.20; found: C 54.88, H 6.43, N 21.50.

*4.4.3. 2-(2-Acetamidophenyl)-N-(3-hydrazinyl-3-oxopropyl)acetamide (**11b**).* The product was obtained as a white solid (mp 204–206°C) in 86% yield. IR (KBr): 3432.09, 3366.21, 3320.90, 3222.65 (NH_2 and NH amide), 1666.91, 1593.01, 1559.48 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 2.17 (s, 3H, $COCH_3$), 2.30 (t, 2H, CH_2CH_2CO), 3.36 (q, 2H, $NHCH_2CH_2$), 4.19 (brs, 2H, NH), 4.51 (s, 2H, $C_6H_4CH_2CO$), 7.00 (m, 2H, Ar), 7.14 (d, 1H, Ar), 7.24 (t, 1H, Ar), 7.28 (s, 1H, NH), 8.33 (t, 1H, NH), 9.08 (s, 1H, NH). ^{13}C NMR (d_6-DMSO): δ = 22.18, 33.58, 36.46, 87.35, 123.75, 123.97, 125.54, 126.31, 129.50, 141.78, 157.73, 169.85, 170.63 ppm. $C_{13}H_{18}N_4O_3$ (278.31): Calcd. C 56.10, H 6.52, N 20.13; found: C 55.87, H 6.81, N 19.89.

*4.4.4. 2-(2-Acetamidophenyl)-N-(4-hydrazinyl-4-oxobutyl)acetamide (**11c**).* The product was obtained as a white solid (mp 195–197°C) in 84% yield. IR (KBr): 3344.24, 3304.18, 3260.00, 3219.07 (NH_2 and NH amide), 1662.11, 1588.61, 1563.41 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 1.69 (m, 2H, $CH_2CH_2CH_2$), 2.04 (t, 2H, CH_2CO), 2.18 (s, 3H, $COCH_3$), 3.14 (q, 2H, CH_2CH_2NH), 4.16 (brs, 2H, NH), 4.51 (s, 2H, $C_6H_4CH_2CO$), 6.97–7.01 (m, 2H, Ar), 7.15–7.24 (m, 3H, 1NH, Ar), 8.34 (t, 1H, NH), 8.97 (s, 1H, NH). ^{13}C NMR (d_6-DMSO): δ = 22.27, 25.83, 31.71, 40.32, 87.44, 123.62, 124.07, 126.27, 129.44, 157.63, 169.96, 171.95 ppm. $C_{14}H_{20}N_4O_3$ (292.33): Calcd. C 57.52, H 6.90, N 19.17; found: C 57.33, H 7.11, N 19.42.

*4.4.5. 2-(2-Acetamidophenyl)-N-(6-hydrazinyl-6-oxohexyl)acetamide (**11d**).* The product was obtained as a white solid (mp 186–188°C) in 90% yield. IR (KBr): 3400.00, 3311.34, 3213.91 (br) (NH_2 and NH amide), 1663.64, 1563.97, 1527.95 (CONH) cm^{-1}. ^1H NMR (d_6-DMSO): δ = 1.20–1.23 (m, 2H, $CH_2CH_2CH_2$), 1.45–1.48 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.00 (t, 2H, CH_2CO), 2.17 (s, 3H, $COCH_3$), 3.13 (q, 2H, CH_2CH_2NH), 4.15–4.45 (br, 2H, NH), 4.50 (s, 2H, $C_6H_4CH_2CO$), 6.98–7.02 (m, 2H, Ar), 7.13–7.33 (m, 3H, NH, Ar), 8.30 (t, 1H, $HNCH_2$), 8.96 (s, 1H, $HNCOCH_3$). ^{13}C NMR (d_6-DMSO): δ = 22.16, 25.50, 26.59, 29.23, 33.92, 40.13, 87.43, 123.68, 123.97, 125.69, 126.26, 129.47, 141.81, 157.81, 169.80, 172.27 ppm. $C_{16}H_{24}N_4O_3$ (320.39): Calcd. C 59.98, H 7.55, N 17.49; found C 60.11, H 7.67, N 17.68.

Acknowledgments

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