

## Synthesis of hydrazone-hydrazone derivatives and their evaluation of antidepressant, sedative and analgesic agents

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### Abstract:

The reaction of cyanoacetylhydrazine (1) with  $\omega$ -bromo(4-methoxyacetophenone) (2) gave the hydrazone-hydrazone derivative 3. Compound 3 reacted with either potassium cyanide or potassium thiocyanide to give the cyanide or thiocyanide derivatives 4a or 4b respectively. The reaction of compound 3 with either hydrazine hydrate or phenylhydrazine gave the hydrazine derivatives 6a or 6b respectively. The latter compounds underwent a series of heterocyclization when react with different reagents to give 1,3,4-triazine and pyridine derivatives. The antidepressant, sedative and analgesic activities of the newly synthesized products were evaluated.

**Keywords:** Antidepressant. hydrazone-hydrazone. pyridine. sedative. 1,3,4-triazine,

### Introduction:

We report here the synthesis of a series of hydrazone-hydrazone derivatives via the reaction of cyanoacetylhydrazine 1 with  $\omega$ -bromo(4-methoxyacetophenone) 2. The hydrazone-hydrazone derivatives have been demonstrated to possess antibacterial, [1-7] anticonvulsant [8-11] and antitubercular activities [9-15]. These observations led us to synthesize novel hydrazone-hydrazone derivatives and to investigate their possible antidepressant, sedative and analgesic activities. It has been reported in the literature [16,17] that hydrazone-hydrazone derivatives can give corresponding hydrazide and aldehyde metabolites whereas the related hydrazides are known to yield carboxylic acids via hydrolytic route. Based on this knowledge, one can expect that the hydrazone-hydrazone derivatives, which were obtained via the reaction of  $\alpha$ -halocarbonyl compounds with hydrazide derivatives capable to form hydrazines linked to the hydrazone-hydrazone moiety

### Materials and methods:

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on a Pye Unicam SP-1000 spectrophotometer. <sup>1</sup>H-NMR spectrum were measured on a Varian EM-390-200 MHz in CD<sub>3</sub>SOCD<sub>3</sub> as solvent using TMS as internal standard, and chemical shifts are expressed as  $\delta$ . Analytical data were obtained from the

Micro Analytical Data Unit at Cairo University, Giza, Egypt.

Synthetic pathways are presented in Schemes 1-2 and physicochemical, spectral data for the newly synthesized compounds are given in Tables 1 and 2. The pharmacological data are indicated through Tables 3, 4 and 5.

### Experimental section:

#### 4-Methoxy- $\omega$ -bromoacetophenone-cyanoacetylhydrazone (3)

To a solution of cyanoacetylhydrazine (1) (2.44 g, 0.02 mol) in 1,4-dioxan (20 mL),  $\omega$ -bromo-(4-methoxyacetophenone) (2) (5.24 g, 0.02 mol) was added. The reaction mixture was stirred at room temperature for 1 hr then poured onto a beaker containing ice/water mixture. The formed solid product was collected by filtration and dried obtaining pale yellow crystals from ethanol to obtain yield 4.77 g

#### 4-methoxy- $\omega$ -cyanoacetophenonecyanoacetylhydrazone (4a), 4-methoxy- $\omega$ -thiocyano-aceto-phenoecyanoacetylhydrazone (4b)

#### General procedure:

To a solution of 3 (0.54 g, 0.0018 mol) in ethanol (25 mL) in a water bath at 60 °C, either potassium cyanide (0.11 g, 0.0018 mol) or potassium thiocyanate (0.17 g, 0.0018 mol) was added with continuous stirring. The reaction mixture was left in the water bath for 30 min at 60 °C then poured onto a beaker containing ice/water

mixture and few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

**(4a):** Pale brown crystals from ethanol. Yield: 0.338 g.

**(4b):** Orange crystals from ethanol. Yield: 0.29 g.

**4-methoxy- $\omega$ -hydrazinoacetophenone-cyanoacetylhydrazone (6a), 4-methoxy- $\omega$ -phenyl-hydrazinoacetophenone-cyanoacetylhydrazone (6b)**

General procedure:

To a solution of compound 3 (1.50 g, 0.005 mol) in ethanol (35 mL) either hydrazine hydrate (0.25 g, 0.005 mol) or phenylhydrazine (0.55 g, 0.005 mol) was added. The reaction mixture was heated under reflux for 3 hrs then poured onto ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

**(6a):** Orange crystals from ethanol, yield: 1.02 g.

**(6b):** Brown crystals from ethanol. Yield: 1.12g.

**$\alpha$ -Benzal-4 methoxy- $\omega$ - hydrazine-acetophenone-cyanoacetylhydrazone(8a) and- $\alpha$ -benzal-4-methoxy- $\omega$ -phenyl-hydrazino-acetophenonecyanoacetyl-hydrazone (8b)**

To a solution of either compound 6a (0.29 g, 0.0012 mol) or 6b (0.36 g, 0.0012 mol) in ethanol (25 mL) containing piperidine (0.5 mL), benzaldehyde (0.11 g, 0.0015 mol) was added. The reaction mixture was heated under reflux for 3hrs then poured onto ice/water mixture containing containing few drops of hydrochloric acid. The formed solid product was collected by filtration.

**8a:** Yellow crystals from ethanol, yield 0.24 g.

**8b:** Orange crystals from ethanol, yield 0.26 g.

**4-Amino-5-H-6-(4-methoxyphenyl)-3-( $\alpha$ -phenylhydrazoneacetonitrilo)-1,2,4-triazine-(10a)**

To a cold solution (0- 5 °C) of compound 6a (0.40 g, 0.0016 mol) in ethanol (50

mL) containing sodium hydroxide (10 mL, 10 %) and a solution of benzenediazonium chloride (0.0016 mol ) [which was prepared by dissolving sodium nitrite (0.16 g, 0.0024 mol) in water, 2 mL was added to a cold solution of aniline (0.15 g, 0.0016 mol ) containing the appropriate amount of hydrochloric acid and with continuous stirring] was added with continuous stirring. The formed solid product was collected by filtration.

**10a:** Pale brown crystals from DMF, yield 0.4 g.

**4-Amino-5-H-6-(4-methoxyphenyl)-3-[ $\alpha$ -(3-cyano-2-hydrazo-4,5,6,7-tetrahydro-benzo-[b]thiophene)acetonitrilo]-1,2,4-triazine(10b), Ethyl-4-amino-5-H-6-(4-methoxyphenyl)-3-[ $\alpha$ (2-hydrazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate)acetonitrilo]-1,2,4-triazine (10c)**

General procedure:

To a cold solution (0-5 °C) of compound 6a (0.49 g, 0.002 mol) in ethanol (50 mL) containing sodium hydroxide solution (10 mL, 10 %) and a solution of either 3-cyano-4,5,6,7-terahydrobenzo[b]-thiophene-2-diazonium chloride 9b (0.002 mol) or ethyl 4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate-2-diazonium chloride 9c (0.002 mol) [which was prepared by dissolving sodium nitrite (0.20 g, 0.003 mol) in water, 2 mL was added to a cold solution of either the 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (0.35 g, 0.002 mol) or the ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (0.42 g, 0.002 mol) dissolved in acetic acid (50 mL) containing the appropriate amount of hydrochloric acid and with continuous stirring] was added with continuous stirring. The formed solid product was collected by filtration and dried.

**10b:** Orange crystals from ethanol, yield 0.71g

**10c:** Brown crystals ethanol, yield 0.63g

**4-Phenylamino-5-H-6-(4-methoxy-phenyl)-3-( $\alpha$ -phenylhydrazoaceto-nitrilo)-1,2,4-triazine (10d)**

To a cold solution (0-5 °C) of compound 6b (0.53 g, 0.0016 mol) in ethanol (50 mL) containing sodium hydroxide (10 mL, 10 %) and a solution of benzenediazonium chloride (0.0016 mol ) [which was prepared by dissolving sodium nitrite (0.17 g, 0.0025 mol) in water, 2 mL was added to a cold solution of aniline (0.15 g, 0.0016 mol ) containing the appropriate amount of hydrochloric acid and with continuous stirring] was added with continuous stirring. The formed solid product was collected by filtration and dried.

**10d:** Reddish brown crystals from ethanol and few drops of dimethylformamide, yield 0.4g

**4-Phenylamino-6-(4-methoxyphenyl)-3-[ $\alpha$ -(3-cyano-2-hydrazo-4,5,6,7-tetrahydrobenzo [b]thiophene)-aceto-nitrilo]-1,2,4-triazine(10e), Ethyl-4-phenylamino-6-(4-methoxy-phenyl)-3-[ $\alpha$ -(2-hydrazo-4,5,6,7-tetrahydrobenzo [b] thiophen-3-carboxylate) acetonitrilo]-1,2,4-triazine (10f)**

General procedure:

To a cold solution (0-5 °C) of compound 6b (0.40 g, 0.0012 mol) in ethanol (50 mL) containing sodium hydroxide solution (10 mL, 10 %) and a solution of either 3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene-2-diazonium chloride 9b (0.0012 mol) or ethyl 4,5,6,7-tetrahydrobenzo[b]thiophen-3-carboxylate-2-diazonium chloride 9c (0.0012 mol) was added with continuous stirring. The formed solid product was collected by filtration and dried.

**10e:** Reddish brown crystals from ethanol and few drops of dimethylformamide. Yield: 0.44g.

**10f:** Pale reddish brown crystals from ethanol. Yield: 0.37g.

**3-Cyano-4,6-dimethyl-2-oxo-1-imino-(4-methoxy- $\omega$ -hydrazinoaceto-phenon-ylidieno)-pyridine (12a), 3-Cyano-6-hydroxy-4-methyl-2-oxo-1-imino(4-**

**methoxy- $\omega$ -hydrazino-acetophenon-ylidieno) Pyridine (12b)**

**General Procedure:**

To a solution of compound 6a (0.52 g, 0.0021 mol) in ethanol (20 mL) containing piperidine (0.5 mL), either acetylacetone (0.21 g, 0.0021 mol) or ethyl acetoacetate (0.27 g, 0.0021 mol) was added. The reaction mixture was heated under reflux for 3 hrs then poured onto a beaker containing ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

**12a:** Brown crystals from ethanol. Yield:0.37g.

**12b:** Brown crystals from ethanol. Yield: 0.38 g

**Pharmacological activity:**

**Animals-** Swiss albino mice of either sex, weighing 20-25 g of body weight, aged 6-8 weeks, were supplied by the Animal House at National Research Centre, Giza, Egypt. Animals were maintained under 12/12 hr light/dark cycle at 20  $\pm$  2 and fed with standard laboratory diet and water *ad libitum*. In accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985) groups of 6 mice for group were used in all experiments.

**Screening for antidepressant activity:**

Porsolt's forced-swimming test- Each mouse was placed individually in a glass cylinder (diameter 12 cm, height 24 cm) filled with water at a height of 12 cm. Water temperature was maintained at 22-23 °C. The animal was forced to swim for 6 min and the duration of immobility was measured. The mouse was considered as immobile when it stopped struggling and moved only to remain floating in the water, keeping its head above water. The floating time, which was the measure of despair (21), was recorded 60 min after treatment with each drug (15 or 30 mgkg<sup>-1</sup>, i.p.), saline or imipramine (15 mgkg<sup>-1</sup>, i.p.). Tested compounds were dissolved using few drops of Tween 80 and further dilutions were done to obtain the necessary

**Table 1: Physicochemical data for the newly synthesized compounds**

Comp.	Mol. Formula	Mol.Wt	Elemental analysis				Yield	m.p.
			Calcd.(found)					
			C	H	N	S	%	°C
<b>3</b>	C <sub>12</sub> H <sub>12</sub> BrN <sub>3</sub> O <sub>2</sub>	310.15	46.47	3.89	13.54	-	77	220-224
			46.73	4.62	13.75			
<b>4a</b>	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	256.26	60.93	4.71	21.86	-	73	221-224
			61.21	4.99	22.02			
<b>4b</b>	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	288.32	54.15	4.19	19.43	11.11	56	164-166
			54.39	4.27	19.21	11.40		
<b>6a</b>	C <sub>12</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub>	261.28	55.16	5.78	26.80	-	78	177-180
			55.31	6.25	27.06			
<b>6b</b>	C <sub>18</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub>	337.38	64.08	5.67	20.75	-	66	98
			64.36	5.84	20.93			
<b>8a</b>	C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub>	349.39	65.31	5.48	20.04	-	58	188-190
			65.49	5.81	19.75			
<b>8b</b>	C <sub>25</sub> H <sub>23</sub> N <sub>5</sub> O <sub>2</sub>	425.48	70.57	5.44	16.45	-	51	170-172
			70.27	5.57	16.72			
<b>10a</b>	C <sub>18</sub> H <sub>17</sub> N <sub>7</sub> O	347.38	62.23	4.93	28.22	-	74	140-141
			62.52	5.31	28.48			
<b>10b</b>	C <sub>21</sub> H <sub>20</sub> N <sub>8</sub> OS	432.50	58.31	4.66	25.90	7.41	82	210-213
			58.47	5.03	26.15	7.69		
<b>10c</b>	C <sub>23</sub> H <sub>25</sub> N <sub>7</sub> O <sub>3</sub> S	479.55	57.60	5.25	20.44	6.68	66	160
			57.28	5.49	20.39	6.92		
<b>10d</b>	C <sub>24</sub> H <sub>21</sub> N <sub>7</sub> O	423.47	68.07	4.99	23.15	-	59	211-214
			67.56	5.29	23.41			
<b>10e</b>	C <sub>27</sub> H <sub>24</sub> N <sub>8</sub> OS	508.60	63.76	4.75	22.03	6.30	72	180-182
			63.96	5.06	21.68	5.79		
<b>10f</b>	C <sub>29</sub> H <sub>29</sub> N <sub>7</sub> O <sub>3</sub> S	555.65	62.68	5.26	17.64	5.76	55	>300
			62.76	5.13	17.90	6.04		
<b>12a</b>	C <sub>17</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub>	325.36	62.75	5.88	21.52	-	54	256-258
			63.01	6.19	21.82			
<b>12b</b>	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> O <sub>3</sub>	327.34	58.71	5.23	21.39	-	55	188-191
			58.43	5.44	21.53			

doses. During our measurements the tested compounds were dissolved using few drops of Tween 80 and further dilution was done using saline to get the necessary doses. The negative control is the vehicle solution (Tween 80 in saline).

#### Screening for sedative effect:

Mice were observed in a commercially available motor activity apparatus (Ugo Basel, Italy) in which locomotor and exploratory activity could be monitored. In these experiments, each mouse was intraperitoneally injected with the drug at

30 mgkg<sup>-1</sup> and 30 min later was placed in the activity monitor in which activity was monitored for 6 min.

#### Screening for analgesic effect:

Acetic acid-induced writhing was performed for separate groups of 6 mice each were i.p. administered vehicle, compounds 3, 4a,b, 6a,b, 8a,b, 10a-f, 12a,b (15 and 30 mgkg<sup>-1</sup>) or indomethacin (20 mgkg<sup>-1</sup>). After 30 min pretreatment interval, an i.p. injection of 0.6% acetic acid was administered (Koster et al, 1959). Each mouse was then placed in an

**Table 2: Spectral data for the newly synthesized compounds.**

Compound	Spectral data
<b>3</b>	IR, $\nu/\text{cm}^{-1}$ : 1644 (C=C), 1688 (C=O), 2261 (CN), 2979 (CH <sub>3</sub> ), 3050 (CH aromatic), 3342-3479 (NH). <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ), $\delta$ : 3.01 (s, 3H, CH <sub>3</sub> ), 4.31, 4.72 (2s, 4H, CH <sub>2</sub> ), 6.50-6.76 (m, 4H, C <sub>6</sub> H <sub>4</sub> ), 11.46 (s, 1H, NH) D <sub>2</sub> O exchangeable
<b>4a</b>	IR, $\nu/\text{cm}^{-1}$ : 1687 (C=O), 2220,2258 (2CN), 3044 (CH aromatic), 3341-3476 (NH). <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ), $\delta$ : 3.03 (s, 3H, CH <sub>3</sub> ), 4.43, 5.04 (2s, 4H, CH <sub>2</sub> ), 7.31-7.42 (m, 4H, C <sub>6</sub> H <sub>4</sub> ), 10.78 (s, 1H, NH) D <sub>2</sub> O exchangeable
<b>4b</b>	IR, $\nu/\text{cm}^{-1}$ : 1686 (C=O), 2222, 2258 (2CN), 2925, 2965(CH <sub>2</sub> , CH <sub>3</sub> ), 3060 (CH aromatic), 3242-3449 (NH) <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ), $\delta$ : 3.03 (s, 3H, CH <sub>3</sub> ), 4.44, 5.06 (2s, 4H, 2CH <sub>2</sub> ), 7.39-7.62 (m, 4H, C <sub>6</sub> H <sub>4</sub> ), 10.62 (s, 1H, NH). D <sub>2</sub> O exchangeable
<b>6a</b>	IR, $\nu/\text{cm}^{-1}$ : 1607 (C=C), 1688 (C=O), 2203 (CN), 2918(CH <sub>3</sub> ), 3027 (CH aromatic), 3204-3400 (2NH, NH <sub>2</sub> ). <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ), $\delta$ : 2.51 (s, 3H, CH <sub>3</sub> ), 3.39, 4.23 (2s, 4H, 2CH <sub>2</sub> ), 4.82 (s, 2H, NH <sub>2</sub> ), 6.93-7.42 (m, 4H, C <sub>6</sub> H <sub>4</sub> ), 9.26, 10.40 (2s, 2H, 2NH) D <sub>2</sub> O exchangeable
<b>6b</b>	IR, $\nu/\text{cm}^{-1}$ : 1600 (C=C), 1687 (C=O), 2250 (CN), 2969(CH <sub>3</sub> ), 3047 (CH aromatic), 3322-3475 (2NH, NH <sub>2</sub> ). <sup>1</sup> H NMR $\delta$ : 3.03 (s, 3H, CH <sub>3</sub> ), 3.38, 4.37 (2s, 4H, 2CH <sub>2</sub> ), 6.79-7.49 (m, 9H, C <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>4</sub> ), 10.31, 10.80, 11.21 (3s, 3H, 3NH) D <sub>2</sub> O exchangeable
<b>8a</b>	IR, $\nu/\text{cm}^{-1}$ : 1642 (C=C), 1687 (C=O), 2246 (CN), 2921(CH <sub>3</sub> ), 3052 (CH aromatic), 3338-3488 (2NH, NH <sub>2</sub> ). <sup>1</sup> H NMR $\delta$ : 3.11 (s, 3H, CH <sub>3</sub> ), 3.38 (s, 2H, CH <sub>2</sub> ), 4.83 (s,2H, NH <sub>2</sub> ), 6.01 (s, 1H, =CH), 7.29-7.36 (m, 9H, C <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>4</sub> ), 8.21, 9.55 (2s, 2H, 2NH).
<b>8b</b>	IR, $\nu/\text{cm}^{-1}$ : 1636 (C=C), 1689 (C=O), 2246 (CN), 2948 (CH <sub>3</sub> ), 3053 (CH aromatic), 3328-3481 (3NH) <sup>1</sup> H NMR $\delta$ : 3.07 (s, 3H, CH <sub>3</sub> ), 3.44 (s, 2H, CH <sub>2</sub> ), 7.27-7.42 (m, 15H, =CH, 2C <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>4</sub> ), 9.09, 10.57, 10.89 (3s, 3H, 3NH).
<b>10a</b>	IR, $\nu/\text{cm}^{-1}$ : 1638 (C=C), 2234 (CN), 2873, 2948 (CH <sub>2</sub> , CH <sub>3</sub> ), 3054 (CH aromatic), 3322-3450 (NH, NH <sub>2</sub> ) <sup>1</sup> H NMR $\delta$ : 3.11 (s, 3H, CH <sub>3</sub> ), 3.39 (s, 2H, CH <sub>2</sub> ), 4.32 (s, 2H, NH <sub>2</sub> ), 7.26-7.48 (m, 9H, C <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>4</sub> ), 10.46 (s, 1H, NH)
<b>10b</b>	IR, $\nu/\text{cm}^{-1}$ : 1635 (C=C), 2220, 2253 (2CN), 2948 (CH <sub>3</sub> ), 3053 (CH aromatic), 3421-3458 (NH, NH <sub>2</sub> ) <sup>1</sup> H NMR $\delta$ : 1.62-2.35 (m, 8H, cyclohexene), 3.09 (s, 3H, CH <sub>3</sub> ), 3.69 (s,

2H, CH<sub>2</sub>), 4.83 (s, 2H, NH<sub>2</sub>), 6.98- 7.39 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 9.92 (s, 1H, NH).

- 10c** IR,  $\nu/\text{cm}^{-1}$ : 1711 (C=O), 2213 (CN), 2860, 2934, 2976 (CH<sub>2</sub>, 2CH<sub>3</sub>), 3287-3400 (NH, NH<sub>2</sub>)  
<sup>1</sup>H NMR  $\delta$ : 1.07-1.92 (m, 8H, cyclohexene), 1.77 (t, 3H, CH<sub>3</sub>), 3.14 (s, 3H, CH<sub>3</sub>), 3.38 (s, 2H, CH<sub>2</sub>), 4.24 (q, 2H, CH<sub>2</sub>), 4.99 (s, 2H, NH<sub>2</sub>), 6.50-8.08 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 9.88 (s, 1H, NH).
- 10d** IR,  $\nu/\text{cm}^{-1}$ : 1632 (C=C), 2220 (CN), 2921, 2988 (CH<sub>2</sub>, CH<sub>3</sub>), 3060 (CH aromatic), 3422-3545 (2NH)  
<sup>1</sup>H NMR  $\delta$ : 3.11 (s, 3H, CH<sub>3</sub>), 3.40 (s, 2H, CH<sub>2</sub>), 6.79-7.52 (m, 14H, 2C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>4</sub>), 8.15, 9.05 (s, 2H, 2NH).
- 10e** IR,  $\nu/\text{cm}^{-1}$ : 1621 (C=C), 2222, 2247 (2CN), 2930 (CH<sub>3</sub>), 3042 (CH aromatic), 3435-3488 (2NH)  
<sup>1</sup>H NMR  $\delta$ : 1.65-2.37 (m, 8H, cyclohexene), 3.22 (s, 3H, CH<sub>3</sub>), 3.60 (s, 2H, CH<sub>2</sub>), 6.97- 8.32 (m, 9H, C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>4</sub>), 9.84, 10.00 (s, 2H, 2NH).
- 10f** IR,  $\nu/\text{cm}^{-1}$ : 1711 (C=O), 2213 (CN), 2852, 2944, 2962 (CH<sub>2</sub>, 2CH<sub>3</sub>), 3287-3400 (2NH)  
<sup>1</sup>H NMR  $\delta$ : 1.07-1.92 (m, 8H, cyclohexene), 2.51 (s, 3H, CH<sub>3</sub>), 2.77 (t, 3H, CH<sub>3</sub>), 3.36 (s, 2H, CH<sub>2</sub>), 4.24 (q, 2H, CH<sub>2</sub>), 6.50-8.08 (m, 9H, C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>4</sub>), 9.88, 10.30 (2s, 2H, 2NH).
- 12a** IR,  $\nu/\text{cm}^{-1}$ : 1631 (C=C), 1687 (C=O), 2227 (CN), 2882, 2966 (CH<sub>2</sub>, CH<sub>3</sub>), 3050 (CH aromatic), 3312-3430 (NH, NH<sub>2</sub>)  
<sup>1</sup>H NMR  $\delta$ : 2.36, 2.52, 3.07 (3s, 9H, 3CH<sub>3</sub>), 3.41 (s, 2H, CH<sub>2</sub>), 5.11 (s, 2H, NH<sub>2</sub>), 6.09 (s, 1H, pyridine H-3), 6.93-7.39 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 10.11 (s, H, NH).
- 12b** IR,  $\nu/\text{cm}^{-1}$ : 1630 (C=C), 1683 (C=O), 2222 (CN), 2880, 2975 (CH<sub>2</sub>, CH<sub>3</sub>), 3057 (CH aromatic), 3316-3569 (NH, NH<sub>2</sub>, OH)  
<sup>1</sup>H NMR  $\delta$ : 2.77, 3.28 (3s, 6H, 2CH<sub>3</sub>), 3.65 (s, 2H, CH<sub>2</sub>), 4.85 (s, 2H, NH<sub>2</sub>), 6.07 (s, 1H, pyridine H-3), 6.88-7.34 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 10.23, (s, H, NH), 12.09 (s, 1H, OH).

individual clear plastic observational chamber and the total number of writhes (constriction of abdomen, twisting of trunk and extension of hind legs) made by each mouse was counted for 30 min after acetic acid administration.

**Statistics:**

Data are presented as mean  $\pm$  SE. Data were analyzed by ANOVA followed by Duncan and multiple group comparison

test. A probability value less than 0.05 was considered statistically significant.

**Pharmacology:**

In the present work, the activity of the novel synthesized hydrazide-hydrazone derivatives as antidepressant, sedative or analgesic agents was investigated.

**Screening for antidepressant activity**

After 60 min of i.p. administration, some compounds (3, 4a,b, 8a, 10a-f, 12a and

**Table 3: Effect of tested compounds on the duration of immobility in the Porsolt's forced-swimming test**

Treatment	Duration of immobility (floating time in seconds) (measure of despair)
Saline	289.9 ± 7.1
Imipramine (15 mg/kg)	237.0 ± 14.0*
Compound <b>3</b> (15 mg/kg)	280.7 ± 10.4
Compound <b>3</b> (30 mg/kg)	265.5 ± 15.8
Compound <b>4a</b> (15 mg/kg)	269.31 ± 8.6
Compound <b>4a</b> (30 mg/kg)	260.1 ± 10.3
Compound <b>6a</b> (15 mg/kg)	273.7 ± 8.5
Compound <b>6b</b> (30 mg/kg)	269.7 ± 15.6
Compound <b>8a</b> (15 mg/kg)	286.8 ± 7.8
Compound <b>8a</b> (30 mg/kg)	270.3 ± 13.6
Compound <b>10a</b> (15 mg/kg)	288.9 ± 13.8
Compound <b>10a</b> (30 mg/kg)	262.7 ± 17.6
Compound <b>10b</b> (15 mg/kg)	288.8 ± 7.8
Compound <b>10b</b> (30 mg/kg)	222.3 ± 13.6
Compound <b>10c</b> (15 mg/kg)	284.9 ± 13.8
Compound <b>10c</b> (30 mg/kg)	304.0 ± 9.4
Compound <b>10d</b> (15 mg/kg)	289.8 ± 7.8
Compound <b>10d</b> (30 mg/kg)	274.3 ± 18.6
Compound <b>10e</b> (15 mg/kg)	286.9 ± 11.8
Compound <b>10e</b> (30 mg/kg)	269.7 ± 14.6
Compound <b>10f</b> (15 mg/kg)	286.8 ± 7.8
Compound <b>10f</b> (30 mg/kg)	280.3 ± 13.6
Compound <b>12a</b> (15 mg/kg)	283.9 ± 11.8
Compound <b>12a</b> (30 mg/kg)	274.7 ± 13.6
Compound <b>12b</b> (15 mg/kg)	286.8 ± 7.8
Compound <b>12b</b> (30 mg/kg)	277.3 ± 15.6

**Table 4: Effect of tested compounds on the number of exploratory movements\* in mice**

Treatment	Number of movements
Saline	27.8 ± 2.3*
Compound <b>3</b> (30 mg/kg)	34.3 ± 3.9*
Compound <b>4a</b> (30 mg/kg)	26.0 ± 2.9
Compound <b>4b</b> (30 mg/kg)	50.3 ± 1.0*
Compound <b>6a</b> (30 mg/kg)	32.3 ± 2.4*
Compound <b>6b</b> (30 mg/kg)	34.3 ± 3.9*
Compound <b>8a</b> (30 mg/kg)	30.3 ± 2.4*
Compound <b>8b</b> (30 mg/kg)	70.5 ± 3.9*
Compound <b>10a</b> (30 mg/kg)	34.3 ± 2.9*
Compound <b>10b</b> (30 mg/kg)	20.0 ± 1.9
Compound <b>10c</b> (30 mg/kg)	44.3 ± 3.0*
Compound <b>10d</b> (30 mg/kg)	40.3 ± 1.4*
Compound <b>10e</b> (30 mg/kg)	63.5 ± 2.9*
Compound <b>10f</b> (30 mg/kg)	36.3 ± 3.9*
Compound <b>12a</b> (30 mg/kg)	22.0 ± 1.9*
Compound <b>12b</b> (30 mg/kg)	22.0 ± 1.9*

\*Number of movements in 6 minutes.

**Table 5: Percentage of inhibition of the number abdominal constrictions during 30 min caused by i.p. injection of acetic acid in mice**

Compound	Number	% inhibition
Saline	92.8 ± 6.0	
Compound 3 (15 mg/kg)	40.8 ± 4.0*	22.7%
Compound 3 (30 mg/kg)	4.5 ± 0.29*	90.3%
Compound 4a (15 mg/kg)	28.3 ± 3.5*	66.5%
Compound 4a (30 mg/kg)	28.8 ± 1.2*	71.7%
Compound 4b (15 mg/kg)	31.5 ± 2.2*	50.1%
Compound 4b (30 mg/kg)	27.5 ± 3.2*	42.4%
Compound 6a (15 mg/kg)	22.0 ± 4.0*	48.1%
Compound 6b (30 mg/kg)	20.5 ± 2.6*	74.7%
Compound 8a (15 mg/kg)	40.7 ± 6.8	10.9%
Compound 8b (30 mg/kg)	32.3 ± 4.1*	32.3%
Compound 10a (15 mg/kg)	24.3 ± 3.5*	20.5%
Compound 10a (30 mg/kg)	36.8 ± 1.2*	80.7%
Compound 10b (15 mg/kg)	33.5 ± 2.2*	40.1%
Compound 10b (30 mg/kg)	20.5 ± 3.2*	32.4%
Compound 10c (15 mg/kg)	30.0 ± 4.0*	22.1%
Compound 10c (30 mg/kg)	26.5 ± 2.6*	80.7%
Compound 10d (15 mg/kg)	80.7 ± 6.8	14.9%
Compound 10d (30 mg/kg)	52.3 ± 4.1*	28.3%
Compound 10f (15 mg/kg)	20.3 ± 3.5*	44.5%
Compound 10f (30 mg/kg)	22.8 ± 1.2*	23.7%
Compound 12a (15 mg/kg)	30.5 ± 2.2*	52.1%
Compound 12a (30 mg/kg)	28.5 ± 3.2*	20.4%
Compound 12b (15 mg/kg)	44.0 ± 4.0*	48.1%
Compound 12b (30 mg/kg)	20.5 ± 2.6*	70.7%
Indomethacin (20 mg/kg)	50.3 ± 5.4*	45.8%

12b) showed mild non-significant antidepressant activity at high doses and were active, compared with the control group, using saline as negative control. The rest of compounds failed to display antidepressant properties in the swimming test (Table 3).

#### Screening for sedative activity

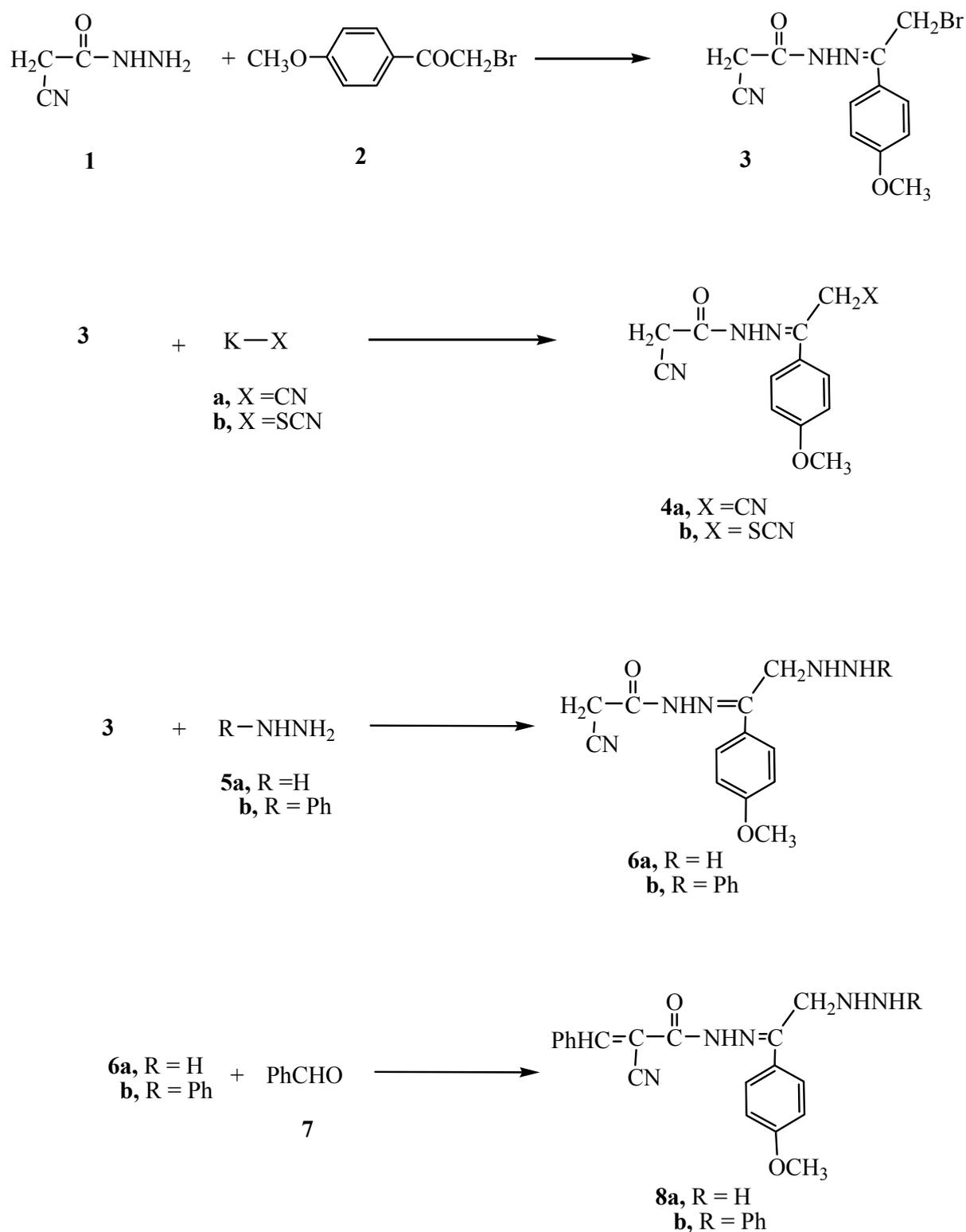
Compounds 4a, 4b and 10b showed less exploratory movements compared with saline treated group (Table 4). All tested compounds at the two doses (15 or 30 mgkg<sup>-1</sup>), except the lower dose of 8b, significantly reduced the number of

#### Results and discussion:-

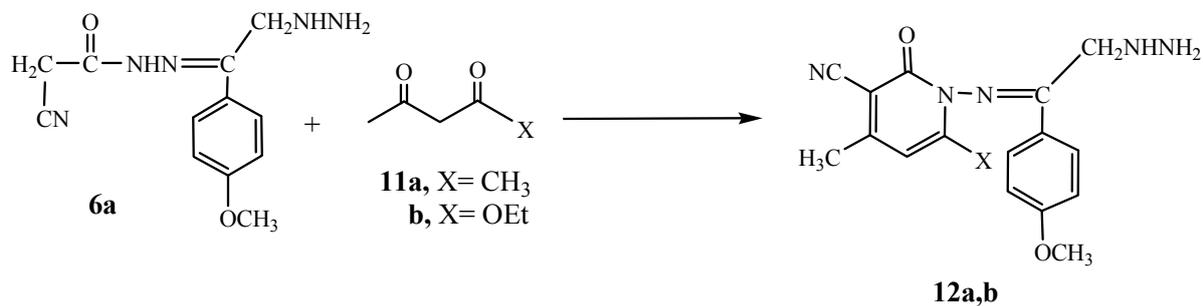
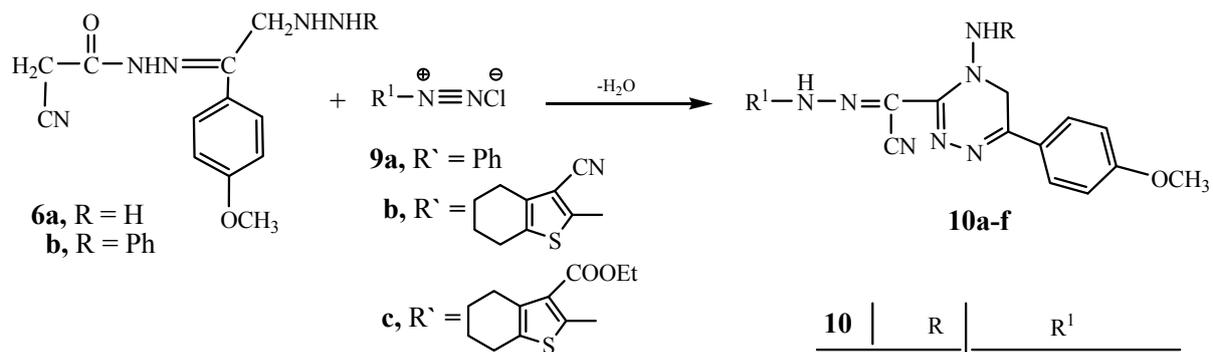
Recently our research group was interested through the uses of hydrazides and hydrazide-hydrazones in heterocyclic

abdominal writhes induced by i.p. injection of acetic acid in mice (Table 5). Compound 3 (at higher concentration) was the most potent in this respect, inhibiting the number of abdominal writhes by 90.3%, at high doses (30 mgkg<sup>-1</sup>), compared with the saline as control negative group. Meanwhile, compounds 4a, 6b, 10c and 12b at high doses inhibited the number of abdominal writhes by 71.7, 74.7, 80.7 and 70.7 %, respectively. These compounds, at low and high doses, were even more potent than indomethacin in this respect.

synthesis [18]. In continuation to this work, we report here the reaction of cyanoacetylhydrazine (1) with ω-bromo-(4-methoxyacetophenone) (2) in 1,4-

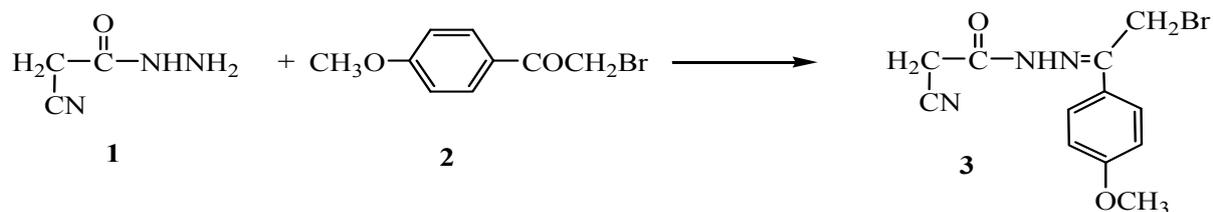


Scheme 1



Scheme 2

Graphical abstracts



dioxan which gave the condensed product 3. Structure of compound 3 was based on analytical and spectral data. Thus, the  $^1\text{H-NMR}$  showed a singlet at  $\delta$  3.01 for the  $\text{CH}_3$ , two singlets at  $\delta$  4.31, 4.72 for the two  $\text{CH}_2$  groups, a multiplet at  $\delta$  6.50-7.76 for the  $\text{C}_6\text{H}_4$  group and a singlet at  $\delta$  11.46 ( $\text{D}_2\text{O}$  exchangeable) for the  $\text{NH}$  group. The reactivity of compound 3 towards chemical reagents was studied. Thus, the reaction of 3 with either potassium cyanide or potassium thiocyanate gave either the cyanide or thiocyanate derivatives 4a and 4b, respectively.

The reaction of compound 3 with either hydrazine hydrate (5a) or phenylhydrazine (5b) gave the hydrazine derivatives 6a and 6b, respectively. Analytical and spectral data of the reaction products are in agree with the proposed structures (see experimental section). The reaction of either 6a or 6b with benzaldehyde (7) gave the benzal derivatives 8a and 8b, respectively. On the other hand, the reaction of either 4a or 4b with either benzenediazonium chloride (9a) 3-cyano-4,5,6,7-tetrahydrobenzo-[b]-thiophene-2-diazonium chloride (9b) or ethyl3-cyano-4,5,6,7-tetrahydro-benzo-[b]thiophene-3-carboxylate-2-diazonium chloride (9c) gave the 3-( $\alpha$ -hydrazoacetonitrilo)-1,2,4-triazine derivatives 10a-f, respectively. The analytical and spectral data of the latter reaction products are in consistent with the proposed structures. Thus the  $^1\text{H}$  NMR spectrum of compound 10a (as an example) showed the presence of a singlet at  $\delta$  3.11 ppm due to the presence of the  $\text{CH}_3$  group, a singlet at  $\delta$  3.30 ppm due to the presence of the  $\text{CH}_2$  group, a multiplet at  $\delta$  7.26-7.48 ppm corresponding to the  $\text{C}_6\text{H}_5$  and  $\text{C}_6\text{H}_4$  groups and a broad singlet ( $\text{D}_2\text{O}$  exchangeable) at  $\delta$  10.46 ppm due to the presence of the  $\text{NH}$  group.

The reaction of compound 6a with either acetylacetone (9a) or ethyl acetoacetate (9b) gave the 6-oxopyridine derivatives 12a and 12b, respectively. Structures of the latter products were based on analytical

and spectral data (see experimental section).

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