

## Synthesis of some new 2,3-disubstituted-4(3H)quinazolinone derivatives

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### Abstract

Quinazolinones are interesting materials because of their valuable biological effects. In this study some new 2,3-disubstituted-4(3H)quinazolinone derivatives were synthesized from anthranilic acid in six steps by introducing a new chiral center to the aliphatic side chain of the quinazolinone. In the last step, a single acylation on the hydrazine moiety afforded final compounds. The structures of compounds were confirmed by IR, <sup>1</sup>HNMR and Mass spectra.

**Keywords:** Anthranilic acid; 4(3H)-Quinazolinone; Synthesis

### INTRODUCTION

Synthesis of different classes of heterocyclic molecules is one of the most important targets in the synthetic organic chemistry. Among the nitrogen-containing heterocyclic compounds, quinazolinones (Fig. 1) have attracted interest of many researchers because, introduction of various substituents to different positions of quinazolinones have produced compounds with valuable biological activities.

Some of their most frequently reported biological properties include cytotoxic, antibacterial, antifungal, anticonvulsant, antitubercular, anti-HIV, antiviral, anti-inflammatory and antihistaminic activities (1-5). Other properties of quinazolinones which have been reported in the literature are antihelminthic, CNS depressant, antidiabetic, antiallergic, antihistaminic, analgesic and hypolipidemic effects (6-10).

Quinazolinones are also the main component of nearly 150 natural alkaloids existing in some families of plants, animals and microorganisms (11). Febrifugine and isofebrifugine which are known as antimalarial agents, are two wellknown natural alkaloids with quinazolinone structure (Fig. 2) (3).

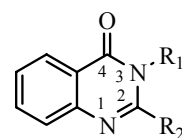
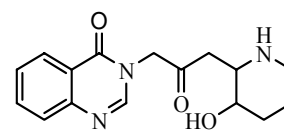
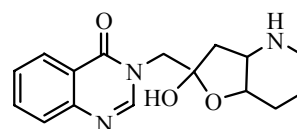


Fig. 1. 4(3H)-Quinazolinone chemical structure



Febrifugine



Isofebrifugine

Fig. 2. Representative examples of natural quiazolinones

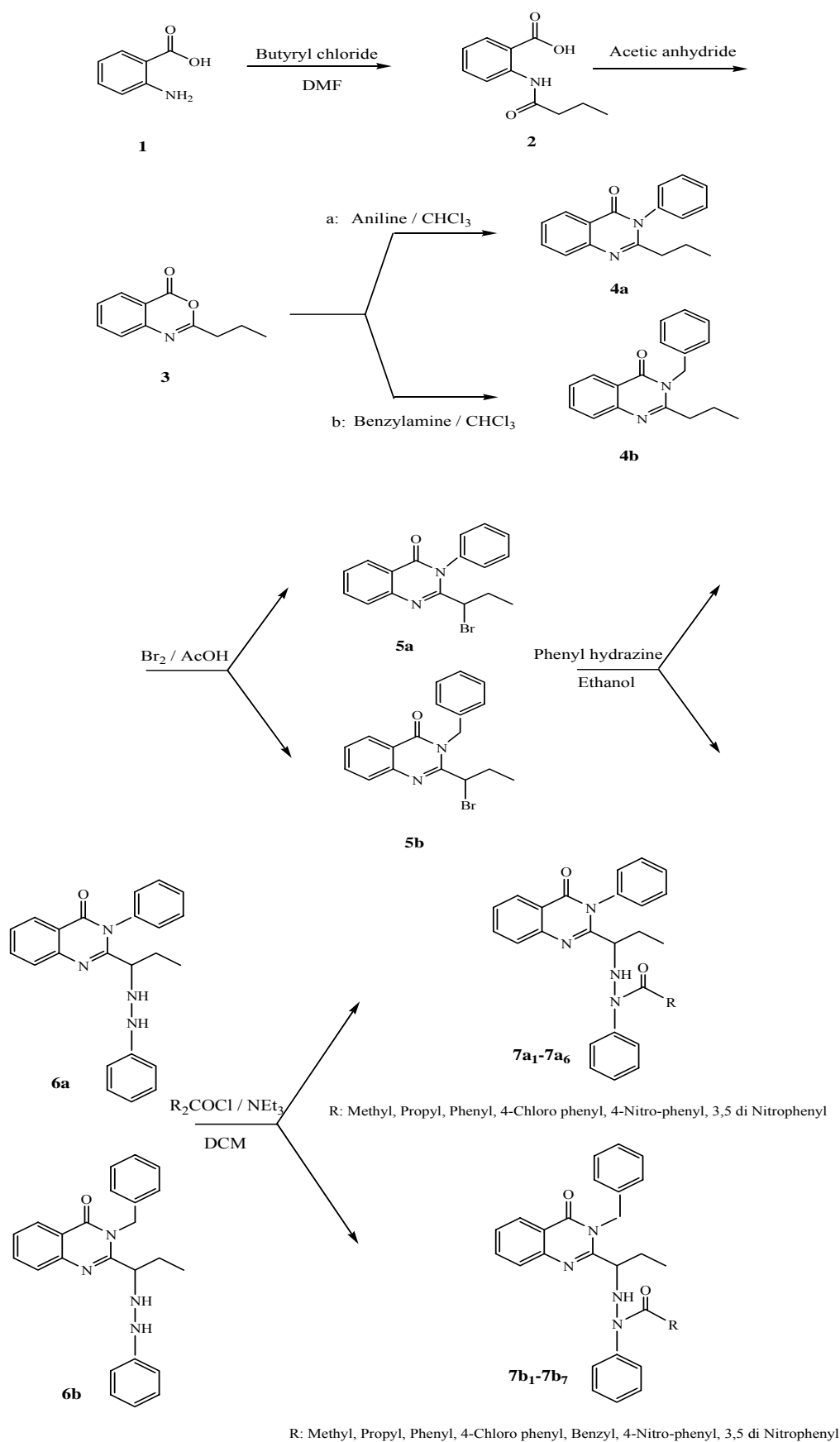
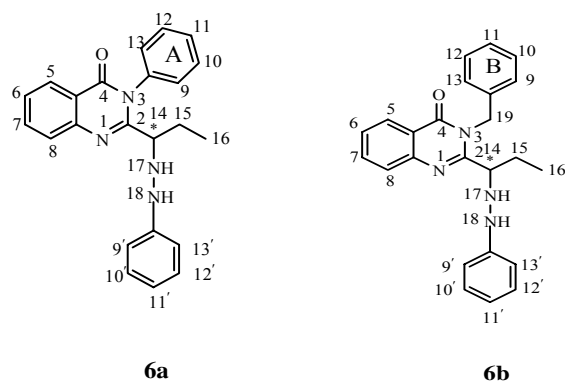
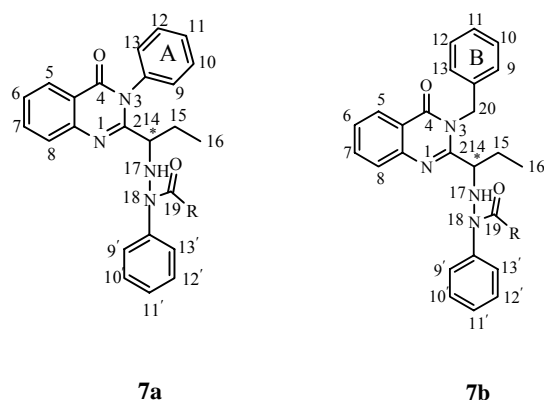


Fig. 3. General reaction scheme for preparation of the final compounds



**Fig. 4.** Chemical structures of compounds **6a** and **6b**



**Fig. 5.** Chemical structures of compounds **7a** and **7b**

containing appropriate substituents, by using benzoxazin-4(1H)-one (benzoxazinone) or by modification of appropriate derivatives of other heterocyclic systems (13). Among various methods for quinazolinone synthesis, application of benzoxazinone has been repeatedly reported.

In the present study, anthranilic acid as starting material was reacted with butyryl chloride to produce N-butyryl anthranilic acid followed by a ring closure in acetic anhydride to afford the corresponding benzoxazinone. Replacement of oxygen in benzoxazinone ring system with primary amines resulted in production of 2,3-disubstituted quinazolinones. Synthesized quinazolinones have either phenyl or benzyl moiety at position 3 (Fig. 1) due to the application of aniline or benzyl amine as primary amines. Substitution of phenyl hydrazine on alkyl side chain at position 2 (Fig. 1) of quinazolinone backbone resulted in production of novel hydrazid derivatives as the first class of final compounds. Subsequently, acylation of these derivatives with various acyl chlorides was performed successfully to obtain second group of novel quinazolinones as substituted hydrazides.

## MATERIALS AND METHODS

### Instrumentation

Melting points were determined in open capillaries using electrothermal 9200 melting point apparatus and are uncorrected. The IR spectra were determined by a WQF-510 FT-IR spectrophotometer using potassium bromide technique.  $^1\text{H}$ NMR spectra were recorded in  $\text{CDCl}_3$  solution on Bruker 400 or 500 MHz spectrometers. Mass spectra were measured on a Shimadzu Mass spectrometer using  $\text{EI}^+$  technique.

### Preparation of compounds

In this study, we have prepared some new 4(3H)-quinazolinone derivatives from anthranilic acid **1** by a six-step procedure (Fig. 3). Anthranilic acid was reacted with butyryl chloride to obtain the corresponding amides. The amides were reacted with acetic anhydride to obtain benzoxazin-4(1H)-one **3** as crystalline product.

The benzoxazinone was subsequently refluxed with two different amines to give the corresponding quinazolinones **4a** and **4b**. The quinazolinones were brominated (**5a**, **5b**) and subsequent treatment with phenyl hydrazine afforded **6a** and **6b**. Finally **6a** and **6b** were reacted with different acid chlorides to obtain compounds **7a<sub>1</sub>-7a<sub>6</sub>** and **7b<sub>1</sub>-7b<sub>7</sub>**. These compounds were purified by column chromatography or preparative thin layer chromatography (PTLC) using several solvent systems. The structures of synthesized compounds were confirmed by IR,  $^1\text{H}$ NMR, and Mass spectra.

All atoms in the chemical structures of the final compounds have been numerically assigned for the ease of interpretation of the  $^1\text{H}$ NMR results (Fig. 4, 5).

## RESULTS

### Details of preparation procedures and chemistry of synthesized compounds

Compounds **2** and **3** were prepared as described by Eissa and coworkers (14). Compound **4a** was synthesized as reported by Kacker and coworkers (15) and compounds **4b**, **5a** and **5b** were prepared based on the method used by Finer and coworkers (16).

*3-phenyl -2- (1- (2-phenylhydrazinyl) propyl) quinazolin-4(3H)-one (6a)*

Phenylhydrazin (3.62 ml, 0.04 mol) was added to a solution of compound **5a** (3.43 g, 0.01 mol) in ethanol (15 ml). The reaction mixture was refluxed for 6 h. After cooling the mixture, the precipitated product was filtered off and crystallized from ethanol to obtain compound **6a**, as white crystals, yield: 30%. m.p 216-217°C, (Found : M 370, C<sub>23</sub>H<sub>22</sub>N<sub>4</sub>O requires 370)  $\nu_{\max}$ , 3309, 3265 (NH), 3051 (Ar-H), 2931, 2870 (R-H), 1660 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (400 MHz ; CDCl<sub>3</sub>) 8.33 (1H, d, J=8.0 Hz, H-C<sup>5</sup> Ar), 7.83 (1H, t, J=8.0 Hz, H-C<sup>7</sup> Ar), 7.78 (1H, d, J=8.0 Hz, H-C<sup>8</sup> Ar), 7.55 (2H, t, J=6.8 Hz, H-C<sup>10</sup>, H-C<sup>12</sup> Ar), 7.46 (1H, t, J=7.2 Hz, H-C<sup>6</sup> Ar), 7.36 (1H, t, J=7.2 Hz, H-C<sup>11</sup> Ar), 7.28(1H, d, J=7.6 Hz, H-C<sup>9</sup> Ar), 7.18 (2H, t, J=7.6 Hz, H-C<sup>10'</sup>, H-C<sup>12'</sup> Ar), 7.00(1H, d, J=7.6 Hz, H-C<sup>13</sup> Ar), 6.88 (2H, d, J=8.0 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.79 (1H, t, J=7.2 Hz, H-C<sup>11'</sup> Ar), 5.53 (1H, s, H-N<sup>18</sup>), 4.52 (1H, d, J=9.6 Hz, H-N<sup>17</sup>), 3.65-3.75 (1H, m, H-C<sup>14</sup>), 1.59-1.70(1H, m, H-C<sup>15</sup>-H'), 1.40-1.53 (1H, m, H-C<sup>15</sup>-H'), 0.87 (3H, t, J=7.2 Hz, H-C<sup>16</sup>).

*3-benzyl -2- (1- (2-phenylhydrazinyl) propyl) quinazolin-4(3H)-one (6b)*

Phenylhydrazin (3.62 ml, 0.04 mol) and a solution of compound **5b** (3.57 g, 0.01 mol) in ethanol (15 ml) were reacted as described for **6a** to give **6b** as white crystal, yield: 50%. m.p188-189°C, (Found: M 384, C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O requires 384)  $\nu_{\max}$ , 3350, 3284 (NH), 3051 (Ar-H), 2933, 2871 (R-H), 1660 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (400 MHz ; CDCl<sub>3</sub>) 8.34 (1H, d, J=8.0 Hz, H-C<sup>5</sup> Ar), 7.80 (1H, t, J=8.0 Hz, H-C<sup>7</sup> Ar), 7.72 (1H, d, J=8.0 Hz, H-C<sup>8</sup> Ar), 7.52 (1H, t, J=7.2 Hz, H-C<sup>6</sup> Ar), 7.08-7.23 (7H, m, C<sup>19</sup>-C<sub>6</sub>H<sub>5</sub>, H-C<sup>10'</sup>, H-C<sup>12'</sup> Ar), 6.83 (2H, d, J=8.0 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.77(1H, t, J=7.2 Hz, H-C<sup>11'</sup> Ar), 5.48(1H, d, J=16 Hz, H-C<sup>19</sup>-H'), 5.34 (1H, s, H-N<sup>18</sup>), 5.17(1H, d, J=15.6 Hz, H-C<sup>19</sup>-H'), 4.62 (1H, d, J=9.2 Hz, H-N<sup>17</sup>), 4.07-4.17 (1H, m, H-C<sup>14</sup>), 1.48-1.70 (2H, m, H-C<sup>15</sup>), 1.09 (3H, t, J=7.2 Hz, H-C<sup>16</sup>).

*General procedure for the preparation of final compounds 7a<sub>1-6</sub>*

Various acid chlorides (1.1 mmol) were added drop wise to a solution of compound **6a**

(0.37 g, 1 mmol) in dichloromethane (40 ml) and triethylamine (0.21 ml, 1.5 mmol). The reaction mixture was stirred at 0°C for 4-5 h and purified by column or thin layer chromatography to give the final compounds **7a<sub>1-6</sub>** as white or yellow powders, yields: 25-30%.

*N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydrazide (7a<sub>1</sub>)*

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 123-124°C (Found: M 412, C<sub>25</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub> requires 412)  $\nu_{\max}$ , 3257(NH), 3064 (Ar-H), 2964, 2929 (R-H), 1689 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (500 MHz ; CDCl<sub>3</sub>) 8.29 (1H, d, J=5.0 Hz, H-C<sup>5</sup> Ar), 7.75-7.85 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.44-7.55 (3H, m, H-C<sup>10</sup>, H-C<sup>12</sup>, H-C<sup>6</sup>, Ar), 7.25-7.40 (4H, m, H-C<sup>11</sup>, H-C<sup>9</sup>, H-C<sup>10'</sup>, H-C<sup>12'</sup> Ar), 7.10-7.25 (4H, m, H-C<sup>13</sup>, H-C<sup>11'</sup>, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 3.4-3.6 (1H, brs, H-C<sup>14</sup>), 1.8-2.1 (4H, m, C<sup>19</sup>-CH<sub>3</sub>, H-C<sup>15</sup>-H'), 1.5-1.8 (1H, m, H-C<sup>15</sup>-H'), 0.6-0.8 (3H, brs, H-C<sup>16</sup>).

*N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydrazide (7a<sub>2</sub>)*

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 118-119°C (Found: M 440, C<sub>27</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub> requires 440)  $\nu_{\max}$ , 3280 (NH), 3064 (Ar-H), 2929, 2871 (R-H), 1687 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (500 MHz ; CDCl<sub>3</sub>) 8.27 (1H, brs, H-C<sup>5</sup> Ar), 7.70-7.85 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.40-7.55 (4H, m, H-C<sup>10</sup>, H-C<sup>12</sup>, H-C<sup>6</sup>, H-C<sup>11</sup> Ar), 7.22-7.40 (3H, m, H-C<sup>9</sup>, H-C<sup>10'</sup>, H-C<sup>12'</sup> Ar), 7.10-7.22 (4H, m, H-C<sup>13</sup>, H-C<sup>11'</sup>, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.55 (1H, brs, H-N<sup>17</sup>), 3.4-3.5 (1H, brs, H-C<sup>14</sup>), 2.0-2.15 (2H, brs, C<sup>19</sup>-CH<sub>2</sub>), 1.85-1.95 (1H, m, H-C<sup>15</sup>-H'), 1.6-1.7 (3H, m, C<sup>19</sup>-CH<sub>2</sub>-CH<sub>2</sub>, H-C<sup>15</sup>-H'), 0.75-0.85 (3H, brs, C<sup>19</sup>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 0.65-0.75 (3H, brs, H-C<sup>16</sup>).

*N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (7a<sub>3</sub>)*

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 110-111°C (Found: M 474, C<sub>30</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub> requires 474)  $\nu_{\max}$ , 3270 (NH), 3064 (Ar-H), 2966, 2927 (R-H), 1685(C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (400 MHz ; CDCl<sub>3</sub>) 8.31(1H, d, J=8.0 Hz, H-C<sup>5</sup> Ar), 7.75-7.85 (2H, brs, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.35-7.55 (4H,

m, H-C<sup>10</sup>, H-C<sup>12</sup>, H-C<sup>6</sup>, H-C<sup>11</sup> Ar), 7.29 (1H, d, J=7.6 Hz, H-C<sup>9</sup> Ar), 7.04-7.27 (9H, m, C<sup>19</sup>-C<sub>6</sub>H<sub>5</sub>, H-C<sup>10'</sup>, H-C<sup>12'</sup>, H-C<sup>13</sup>, H-C<sup>11'</sup> Ar), 6.99 (2H, d, J=7.2 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.50-6.65 (1H, brs, H-N<sup>17</sup>), 3.56 (1H, t, J=6.4 Hz, H-C<sup>14</sup>), 1.80-1.95 (1H, m, H-C<sup>15</sup>-H'), 1.60-1.75 (1H, m, H-C<sup>15</sup>-H'), 0.68 (3H, t, J=7.2 Hz, H-C<sup>16</sup>).

**4-chloro-N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (7a<sub>4</sub>)**

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 127-128°C (Found: M 509, C<sub>30</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>2</sub> requires 509)  $\nu_{\max}$ , 3251 (NH), 3070 (Ar-H), 2962, 2873 (R-H), 1680 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 8.31 (1H, d, J=8.0 Hz, H-C<sup>5</sup> Ar), 7.77-7.90 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.51 (2H, t, J=8.0 Hz, H-C<sup>10</sup>, H-C<sup>12</sup> Ar), 7.47(1H, t, J=7.2 Hz, H-C<sup>6</sup> Ar), 7.4(1H, t, J=7.6 Hz, H-C<sup>11</sup> Ar), 7.05-7.33(9H, m, H-C<sup>9</sup>, C<sup>19</sup>-C<sub>6</sub>H<sub>4</sub>Cl, H-C<sup>10'</sup>, H-C<sup>12'</sup>, H-C<sup>13</sup>, H-C<sup>11'</sup> Ar), 7.0 (2H, d, J=7.6 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 3.55(1H, t, J=6.4 Hz, H-C<sup>14</sup>), 1.80-1.92 (1H, m, H-C<sup>15</sup>-H'), 1.65-1.80 (1H, m, H-C<sup>15</sup>-H'), 0.69 (3H, t, J=7.2 Hz, H-C<sup>16</sup>).

**4-nitro-N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide(7a<sub>5</sub>)**

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 191-192°C (Found: M 519, C<sub>30</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> requires 519)  $\nu_{\max}$ , 3288 (NH), 3064 (Ar-H), 2966, 2925 (R-H), 1685 (C=O), 1522, 1344 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 8.34 (1H, d, J=7.9 Hz, H-C<sup>5</sup> Ar), 8.02 (2H, d, J=8.3 Hz, C<sup>19</sup>-C-CH-CH Ar), 7.8-7.9 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.5-7.6 (2H, m, H-C<sup>10</sup>, H-C<sup>12</sup> Ar), 7.48 (1H, t, J=7.2 Hz, H-C<sup>6</sup> Ar), 7.43 (1H, t, J=7.5 Hz, H-C<sup>11</sup> Ar), 7.15-7.35 (7H, m, C<sup>19</sup>-C-CH, H-C<sup>9</sup>, H-C<sup>10'</sup>, H-C<sup>12'</sup>, H-C<sup>13</sup>, H-C<sup>11'</sup> Ar), 7.05 (2H, d, J=5.5 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 3.55-3.62 (1H, m, H-C<sup>14</sup>), 1.85-1.97 (1H, m, H-C<sup>15</sup>-H'), 1.65-1.75 (1H, m, H-C<sup>15</sup>-H'), 0.69 (3H, t, J=5.0 Hz, H-C<sup>16</sup>).

**3,5-dinitro-N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (7a<sub>6</sub>)**

The compound was purified by column chromatography (petroleum ether: ethyl

acetate; gradient), m.p 208-209°C (Found: M 564, C<sub>30</sub>H<sub>24</sub>N<sub>6</sub>O<sub>6</sub> requires 564)  $\nu_{\max}$ , 3240 (NH), 3095 (Ar-H), 2968, 2927 (R-H), 1684 (C=O), 1541, 1344 (NO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 8.94 (1H, s, C<sup>19</sup>-C-CH-CNO<sub>2</sub>-CH-CNO<sub>2</sub> Ar), 8.2-8.4 (3H, m, H-C<sup>5</sup>, C<sup>19</sup>-C-CH Ar), 7.8-7.9 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.50-7.64 (3H, m, H-C<sup>10</sup>, H-C<sup>12</sup>, H-C<sup>6</sup>, Ar), 7.47(1H, t, J=7.5 Hz, H-C<sup>11</sup> Ar), 7.05-7.40 (7H, m, H-C<sup>9</sup>, H-C<sup>10'</sup>, H-C<sup>12'</sup>, H-C<sup>13</sup>, H-C<sup>11'</sup>, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 3.5-3.64 (1H, m, H-C<sup>14</sup>), 1.8-2.0 (1H, m, H-C<sup>15</sup>-H), 1.60-1.75 (1H, m, H-C<sup>15</sup>-H), 0.6-0.8 (3H, brs, H-C<sup>16</sup>).

**General procedure for the preparation of final compounds 7b<sub>1-7</sub>**

To a solution of compound **6b** (0.384 g, 1 mmol) in dichloromethane (40 ml) was added triethylamine (0.21 ml, 1.5 mmol) and different acid chlorides (1.1 mmol). The reaction mixture was stirred at 0°C for 4-5 h and was purified by column or thin layer chromatography to give the final compounds **7b<sub>1-7</sub>** as white or yellow powders, yields: 25-30%.

**N'-(1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydrazide (7b<sub>1</sub>)**

The compound was purified by PTLC (chloroform: methanol; 100:1) m.p 149-150°C (Found: M 426, C<sub>26</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub> requires 426)  $\nu_{\max}$ , 3244 (NH), 3064 (Ar-H), 2968, 2870 (R-H), 1674 (C=O) cm<sup>-1</sup>; <sup>1</sup>HNMR  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 8.29 (1H, d, J=7.6 Hz, H-C<sup>5</sup> Ar), 7.65-7.78 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.48(1H, t, J=7.6 Hz, H-C<sup>6</sup> Ar), 7.17-7.40 (6H, m, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 7.12 (2H, d, J=5.6 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.75-6.85 (2H, m, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 6.57 (1H, d, J=5.6 Hz, H-N<sup>17</sup>), 5.57 (1H, d, J=16 Hz, H-C<sup>20</sup>-H'), 4.92 (1H, d, J=15.2 Hz, H-C<sup>20</sup>-H'), 3.85 (1H, dd, J=7.6 Hz, J=6.8 Hz, H-C<sup>14</sup>), 1.90-2.05 (1H, m, H-C<sup>15</sup>-H'), 1.8-1.9 (3H, m, C<sup>19</sup>-CH<sub>3</sub>) 1.6-1.8 (1H, m, H-C<sup>15</sup>-H'), 0.5-0.6 (3H, brs, H-C<sup>16</sup>).

**N'-(1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydrazide (7b<sub>2</sub>)**

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 168-169°C (Found: M 454, C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub> requires 454)  $\nu_{\max}$ , 3246 (NH), 3055 (Ar-H), 2964, 2927

(R-H), 1668 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (500 MHz ;  $\text{CDCl}_3$ ) 8.29 (1H, d,  $J=7.5$  Hz, H-C<sup>5</sup> Ar), 7.6-7.8 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.48 (1H, t,  $J=7.5$  Hz, H-C<sup>6</sup> Ar), 7.2-7.4 (6H, m, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 7.05-7.2 (2H, brs, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.75-6.90 (2H, brs, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 6.5-6.7 (1H, brs, H-N<sup>17</sup>), 5.62 (1H, d,  $J=17.0$  Hz, H-C<sup>20</sup>-H'), 4.88 (1H, d,  $J=14.0$  Hz, H-C<sup>20</sup>-H), 3.80-3.95 (1H, m, H-C<sup>14</sup>), 1.9-2.2 (3H, m, C<sup>19</sup>-CH<sub>2</sub>, H-C<sup>15</sup>-H), 1.5-1.8 (3H, m, H-C<sup>15</sup>-H, C<sup>19</sup>-CH<sub>2</sub>-CH<sub>2</sub>), 0.75-0.90 (3H, brs, C<sup>19</sup>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 0.5-0.7 (3H, brs, H-C<sup>16</sup>).

*N'*- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl) -*N*-phenylbenzohydrazide (**7b<sub>3</sub>**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 166-167°C (Found: M 488, C<sub>31</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub> requires 488)  $\nu_{\text{max}}$ , 3242 (NH), 3057 (Ar-H), 2931, 2873 (R-H)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (400MHz ;  $\text{CDCl}_3$ ) 8.31 (1H, d,  $J=8.0$  Hz, H-C<sup>5</sup> Ar), 7.70-7.80 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.48 (1H, t,  $J=7.6$  Hz, H-C<sup>6</sup> Ar), 7.1-7.3 (11H, m, C<sup>19</sup>-C<sub>6</sub>H<sub>5</sub>, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 7.01 (2H, d,  $J=7.6$  Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.9 (2H, d,  $J=6.4$  Hz, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 6.5-6.7 (1H, brs, H-N<sup>17</sup>), 5.67 (1H, d,  $J=16.4$  Hz, H-C<sup>20</sup>-H'), 4.96 (1H, d,  $J=16$  Hz, H-C<sup>20</sup>-H), 4.05 (1H, t,  $J=6.4$  Hz, H-C<sup>14</sup>), 1.9-2.2 (1H, m, H-C<sup>15</sup>-H), 1.70-1.82 (1H, m, H-C<sup>15</sup>-H), 0.53 (3H, t,  $J=7.2$  Hz, H-C<sup>16</sup>).

*N'*- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-4-chloro-*N*-phenylbenzohydrazide (**7b<sub>4</sub>**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 130-131°C (Found: M 523, C<sub>31</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>2</sub> requires 523)  $\nu_{\text{max}}$ , 3249 (NH), 3068 (Ar-H), 2962, 2873 (R-H), 1680 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (400 MHz ;  $\text{CDCl}_3$ ) 8.32 (1H, d,  $J=8.0$  Hz, H-C<sup>5</sup> Ar), 7.67-7.80 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.5 (1H, t,  $J=6.8$  Hz, H-C<sup>6</sup> Ar), 7.08-7.30 (10H, m, C<sup>19</sup>-C<sub>6</sub>H<sub>4</sub>Cl, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 6.97 (2H, d,  $J=7.2$  Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 6.91 (2H, d,  $J=6.0$  Hz, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 6.59 (1H, d,  $J=7.2$  Hz, H-N<sup>17</sup>), 5.58 (1H, d,  $J=16.4$  Hz, H-C<sup>20</sup>-H'), 5.0 (1H, d,  $J=15.6$  Hz, H-C<sup>20</sup>-H), 3.97-4.1 (1H, m, H-C<sup>14</sup>), 1.85-2.0 (1H, m, H-C<sup>15</sup>-H), 1.65-1.80 (1H, m, H-C<sup>15</sup>-H), 0.55 (3H, t,  $J=7.2$  Hz, H-C<sup>16</sup>).

*N'*- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-*N*,2-diphenylacetohydrazide (**7b<sub>5</sub>**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 165-166°C (Found: M 502, C<sub>32</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub> requires 502)  $\nu_{\text{max}}$ , 3290 (NH), 3055 (Ar-H), 2925, 2852 (R-H), 1676 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (500 MHz ;  $\text{CDCl}_3$ ) 8.2-8.4 (1H, brs, H-C<sup>5</sup> Ar), 7.6-7.8 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.48 (1H, t,  $J=7.5$  Hz, H-C<sup>6</sup> Ar), 7.10-7.45 (9H, m, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup>, C<sup>19</sup>-CH<sub>2</sub>-C-CH-CH-CH Ar), 6.95-7.1 (4H, m, H-C<sup>9'</sup>, H-C<sup>13'</sup>, C<sup>19</sup>-CH<sub>2</sub>-C-CH Ar), 6.75-6.9 (2H, brs, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 5.61 (1H, d,  $J=17$  Hz, H-C<sup>20</sup>-H'), 4.8 (1H, d,  $J=12.5$  Hz, H-C<sup>20</sup>-H), 3.85-3.95 (1H, m, H-C<sup>14</sup>), 3.4-3.6 (2H, brs, C<sup>19</sup>-CH<sub>2</sub>), 1.85-2.0 (1H, m, H-C<sup>15</sup>-H), 1.6-1.8 (1H, m, H-C<sup>15</sup>-H), 0.5-0.6 (3H, brs, H-C<sup>16</sup>).

*N'*- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-4-nitro-*N*-phenylbenzohydrazide (**7b<sub>6</sub>**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 131-132°C (Found: M 533, C<sub>31</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> requires 533)  $\nu_{\text{max}}$ , 3275 (NH), 3064 (Ar-H), 2928, 2871 (R-H), 1674 (C=O), 1522, 1344 (NO<sub>2</sub>)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (500 MHz ;  $\text{CDCl}_3$ ) 8.35 (1H, d,  $J=7.5$  Hz, H-C<sup>5</sup> Ar), 8.04 (2H, d,  $J=8.0$  Hz, C<sup>19</sup>-C-CH-CH-CNO<sub>2</sub> Ar), 7.75-7.85 (2H, m, H-C<sup>7</sup>, H-C<sup>8</sup> Ar), 7.54 (1H, t,  $J=8.0$  Hz, H-C<sup>6</sup> Ar), 7.15-7.40 (8H, m, C<sup>19</sup>-C-CH, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 6.92-7.05 (4H, m, H-C<sup>9'</sup>, H-C<sup>13'</sup>, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 5.5 (1H, d,  $J=15$  Hz, H-C<sup>20</sup>-H'), 5.12 (1H, d,  $J=15$  Hz, H-C<sup>20</sup>-H), 4.0-4.1 (1H, brs, H-C<sup>14</sup>), 1.9-2.0 (1H, m, H-C<sup>15</sup>-H), 1.75-1.9 (1H, m, H-C<sup>15</sup>-H), 0.55-0.65 (3H, brs, H-C<sup>16</sup>).

*N'*- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl) -3, 5- dinitro -*N*- phenylbenzohydrazide (**7b<sub>7</sub>**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 120-121°C (Found: M 578, C<sub>31</sub>H<sub>26</sub>N<sub>6</sub>O<sub>6</sub> requires 578)  $\nu_{\text{max}}$ , 3267 (NH), 3095 (Ar-H), 2927, 2873 (R-H), 1666 (C=O), 1539, 1344 (NO<sub>2</sub>)  $\text{cm}^{-1}$ ;  $^1\text{HNMR}$   $\delta_{\text{H}}$  (500 MHz ;  $\text{CDCl}_3$ ) 8.94 (1H, s, C<sup>19</sup>-C-CH-CNO<sub>2</sub>-CH-CNO<sub>2</sub> Ar), 8.2-8.6 (3H, m, C<sup>19</sup>-C-CH-NO<sub>2</sub>, H-C<sup>5</sup> Ar), 7.80-7.92 (2H, m, H-C<sup>7</sup>,

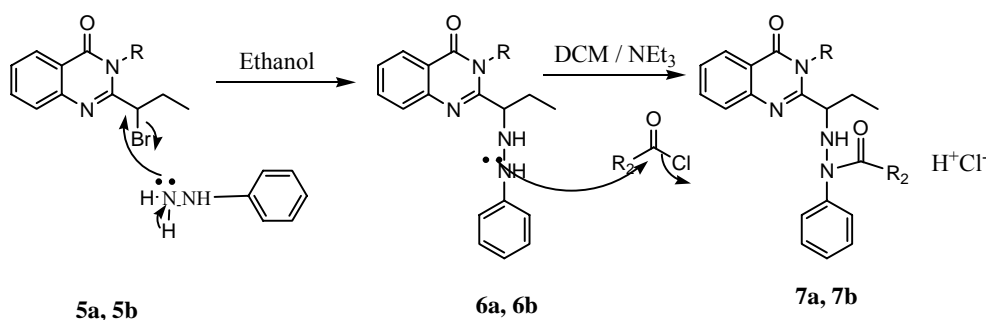


Fig. 6. The proposed mechanism for the production of final compounds

H-C<sup>8</sup> Ar), 7.58 (1H, t, J=7.4 Hz, H-C<sup>6</sup> Ar), 7.27-7.45(6H, m, H-C<sup>10'</sup>, H-C<sup>11'</sup>, H-C<sup>12'</sup>, H-C<sup>10</sup>, H-C<sup>11</sup>, H-C<sup>12</sup> Ar), 7.2 (2H, d, J=6.0 Hz, H-C<sup>9'</sup>, H-C<sup>13'</sup> Ar), 7.1 (2H, d, J=6.0 Hz, H-C<sup>9</sup>, H-C<sup>13</sup> Ar), 5.4-5.6 (1H, brs, H-C<sup>20</sup>-H'), 5.1-5.3 (1H, brs, H-C<sup>20</sup>-H'), 4.0-4.2 (1H, brs, H-C<sup>14</sup>), 1.75-2.0 (1H, m, H-C<sup>15</sup>-H'), 1.5-1.7 (1H, m, H-C<sup>15</sup>-H'), 0.65-0.80 (3H, brs, H-C<sup>16</sup>).

## DISCUSSION

To prepare N-butyryl anthranilic acid **2**, anthranilic acid **1** was treated with butyryl chloride in a nucleophilic substitution reaction.

In the second step, the amide **2** was reacted with acetic anhydride to accelerate ring closure and water removal to get 1,3 benzoxazine-4(1H) **3** as a crystalline product.

In the third step 1,3 benzoxazine-4(1H) **3** was refluxed with two different amines to give the corresponding quinazolinone **4a** and **4b** as a result of a nucleophilic substitution and subsequently dehydration of compound.

Brominated quinazolinones **5a** and **5b** (Fig. 3) were prepared by treating the quinazolinones with bromine in glacial acetic acid. After bromination, a chiral centre was introduced at the position 14 of the propyl side chain. This chiral centre also presents in all compounds synthesized from **5a** and **5b** as illustrated in Fig. 4, 5.

According to <sup>1</sup>HNMR data, aromatic hydrogens at positions 9 and 13 of the phenyl ring (ring A) are seen as two separate doublets in <sup>1</sup>HNMR spectra due to the neighboring effects of this chiral center (Fig. 4, 5). This neighboring effect is also observed for two hydrogens of the benzylic CH<sub>2</sub> next to the ring B and the aliphatic CH<sub>2</sub> at position 15 of the propyl side chain (Fig. 4, 5).

In the fifth step, treatment of brominated quinazolinone **5a** and **5b** with phenyl hydrazine afforded compounds **6a** and **6b**. In this step, the Br atom has been displaced as a leaving group with NH group of phenyl hydrazine as a result of a nucleophilic substitution (Fig. 6).

To obtain the final compounds, compounds **6a** and **6b** were reacted with different acid chlorides via a nucleophilic substitution (Fig. 6).

From two available positions on hydrazine for acylation, substitution of acyl group on nitrogen atom next to the phenyl ring, position 18 (Fig. 5), was confirmed by <sup>1</sup>HNMR. The singlet hydrogen's signal of phenyl-bonded NH has been disappeared after substitution and doublet hydrogen's signal of CH-bonded NH, position 17, has been shifted to down field region due to the deshielding effect of carbonyl functional group

## CONCLUSION

In the current work, quinazolinones as biologically active substances were conjugated with another well known moiety (phenyl hydrazine) in a multi step reaction procedure to produce interesting novel hydrazide derivatives of quinazolinone. These compounds will be subjected to various biological evaluations to investigate their possible activities.

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