

HETEROCYCLES, Vol. 92, No. 2, 2016, pp. 316 - 329. © 2016The Japan Institute of Heterocyclic Chemistry  
Received, 8th December, 2016, Accepted, 7th January, 2016, Published online, 22th January, 2016  
DOI: 10.3987/COM-15-13389

## DESIGN, SYNTHESIS AND ANTICANCER ACTIVITY OF NOVEL 2,3- AND 2,4-DISUBSTITUTED QUINAZOLINE AND QUINAZOLINONE DERIVATIVES

**Maher El-hashash,<sup>1</sup> Jehan Morsy,<sup>2</sup> Mohamed Azab,<sup>1\*</sup> and Naglaa Mahmoud<sup>1</sup>**

<sup>1</sup>Chemistry Department, Faculty of Science, Ain Shams University, Abbasiya, Cairo 11566, Egypt. E-mail: meazab\_ali@yahoo.com

<sup>2</sup>Laboratory of Synthetic Organic Chemistry, Chemistry Department, Faculty of Education, Ain Shams University, Roxy, Cairo 11711, Egypt

**Abstract** - An acetylhydrazide derivative containing a quinazoline nucleus has been utilized to design and synthesize a series of 2,4-disubstituted quinazolines *via* reaction with several carbon electrophiles including 4-methoxybenzaldehyde and carbon disulfide as well as acetyl and benzoyl chloride. Another series of 2,3-disubstituted-4(3*H*)-quinazolinones has been also obtained from reactions of a 3-aminoquinazolin-4(3*H*)-one derivative with other carbon electrophiles, such as chloroacetamide, acetic anhydride, phenyl isocyanate, and ethyl chloroacetate. The structures of the new compounds have been assigned from their spectral data (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS) and elemental analyses. The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against breast cancer, hepatocellular carcinoma, cervical cancer, and human promyelocytic leukemia cell lines. All the tested compounds showed anticancer activity.

## INTRODUCTION

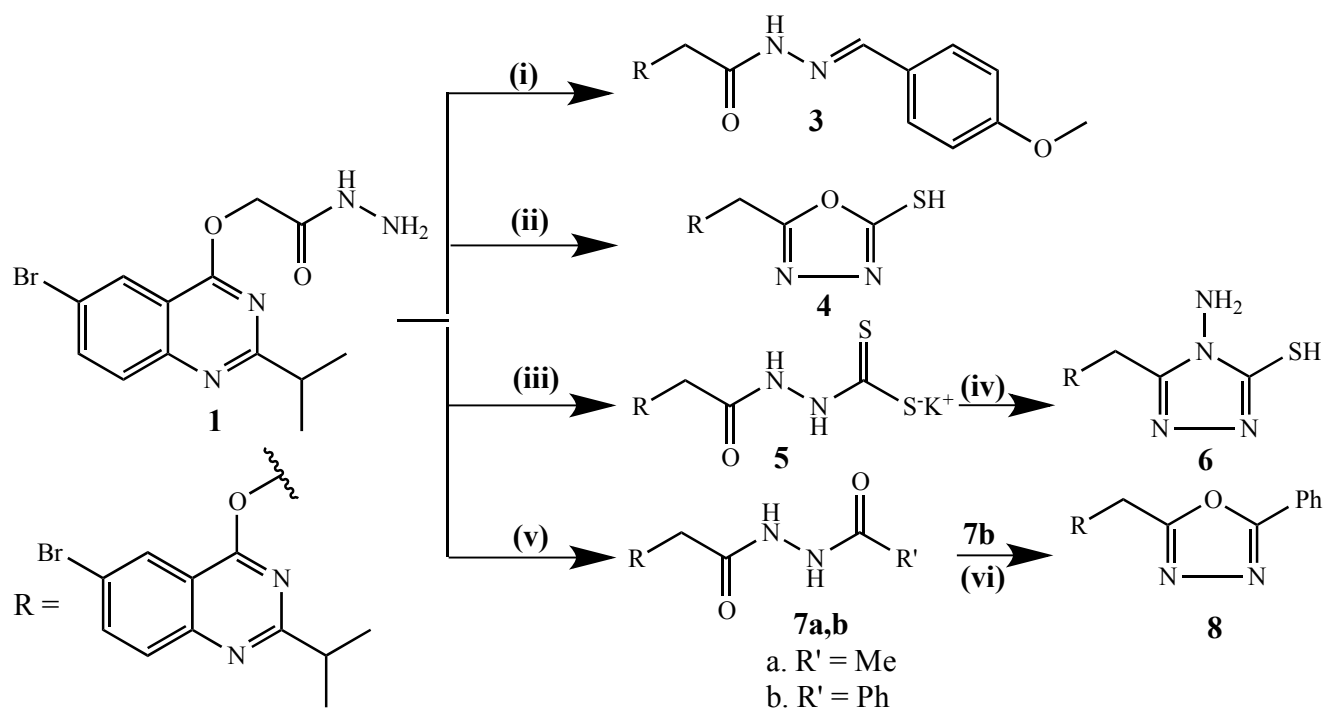
In recent years, quinazolines have emerged as a versatile template for inhibition of a diverse range of receptor tyrosine kinases. The most widely studied of these is the epidermal growth factor receptor (EGFR).<sup>1,2</sup> Exploration of the SAR (structure-activity relationship) of this novel template has led to the discovery of highly potent and selective compounds that target EGFR. These compounds act by competing with ATP for binding at the catalytic domain of tyrosine kinase.<sup>3</sup> These compounds are considered as ATP-competitive inhibitors.

In the present work, we have synthesized a new sub-family of compounds containing 2,3- and 2,4-disubstituted quinazoline cores as expected EGFR inhibitors. Our designing is directed to introducing a variety of ligands with diverse chemical properties hypothesizing that the potency of the new inhibitor might be enhanced by adding an alternative binding group such as isopropyl at position 2. This group is introduced to affect the lipophilicity and hence the activity of the target molecules. We introduced a large moiety at the 3- and/or 4-position of quinazoline so that the bulky group could be oriented deep in the back of the ATP binding site, which makes hydrophobic interactions with the protein. The design of our molecules is based on Noolvi *et al.*<sup>4-6</sup> QSAR studies and is an attempt to obtain active antitumor agents with potential activity and selectivity toward cancerous cells. In the course of identifying various chemical substances which may serve as leads for designing novel antitumor agents, we are particularly interested in the present work with quinazoline derivatives which have been identified as a new class as cancer chemotherapeutic agents.<sup>7-10</sup>

## RESULTS AND DISCUSSION

In continuation of our recent publication,<sup>11</sup> 2-(6-bromo-2-isopropylquinazolin-4-yloxy)acetohydrazide (**1**) and 3-amino-6-bromo-2-isopropylquinazolin-4(3*H*)-one (**2**)<sup>12</sup> have been utilized to construct new substances containing quinazoline core. Thus, the acetylhydrazide containing quinazoline **1** was reacted with *p*-anisaldehyde in refluxing ethanol, in the presence of catalytic amount of piperidine, to afford *N'*-(4-methoxybenzylidene)-2-(6-bromo-2-isopropylquinazolin-4-yloxy)acetylhydrazide (**3**) (Scheme 1).<sup>13</sup> The IR spectrum of compound **3** exhibited absorption bands attributable to C=N and C=O respectively, and its <sup>1</sup>H NMR spectrum showed singlet signal at  $\delta$  8.32 ppm of azomethine proton as well as a singlet at 3.78 of OCH<sub>3</sub>. Boiling hydrazide **1** with carbon disulfide in the presence of potassium hydroxide in ethanol yielded 5-[(6-bromo-2-isopropylquinazolin-4-yloxy)methyl]-1,3,4-oxadiazole-2-thiol (**4**). The IR spectrum of thione **4** showed strong absorption bands at 1243, 1590 cm<sup>-1</sup> attributable to O-C, and C=N respectively. On the other hand, when acid hydrazide **1** was allowed to react with carbon disulfide in presence of potassium hydroxide in ethanol at room temperature,<sup>14</sup> the product was identified as potassium 2-(2-((6-bromo-2-isopropylquinazolin-4-yl)oxy)acetyl)hydrazine-1-carbodithioate (**5**). The IR spectrum of product **5** revealed strong absorption bands at 1620, 1680 and 3412 cm<sup>-1</sup> attributable to C=N, C=O and non bonded NH. Heating **5** with hydrazine hydrate led to the formation of 4-amino-5-[(6-bromo-2-isopropylquinazolin-4-yloxy)methyl]-4*H*-1,2,4-triazole-3-thiol (**6**). The IR spectrum of **6** exhibited absorption bands at 2520 and 3100 cm<sup>-1</sup> due to SH and NH, respectively. Condensation of the hydrazide **1** with acid chlorides such as acetyl and benzoyl chlorides afforded *N'*-[2-(6-bromo-2-isopropylquinazolin-4-yloxy)acetyl]acetyl/benzohydrazide (**7a,b**). IR spectra of compounds **7a,b** exhibit strong absorption bands attributable to C=N, C=O and NH, respectively.

Dropwise addition of phosphorus oxychloride to compound **7b** at 0 °C with continuous stirring, the obtained product was assigned as 2-(((6-bromo-2-isopropylquinazolin-4-yl)oxy)methyl)-5-phenyl-1,3,4-oxadiazole (**8**). The IR spectrum of oxadiazole **8** revealed the lack of bands attributable to C=O and NH. The <sup>1</sup>H NMR spectrum of oxadiazole **8** revealed the disappearance of the two singlets at δ 8.69 and 8.72 ppm of two NH in compound **7b** which are incorporated in cyclization process under the effect of POCl<sub>3</sub>.

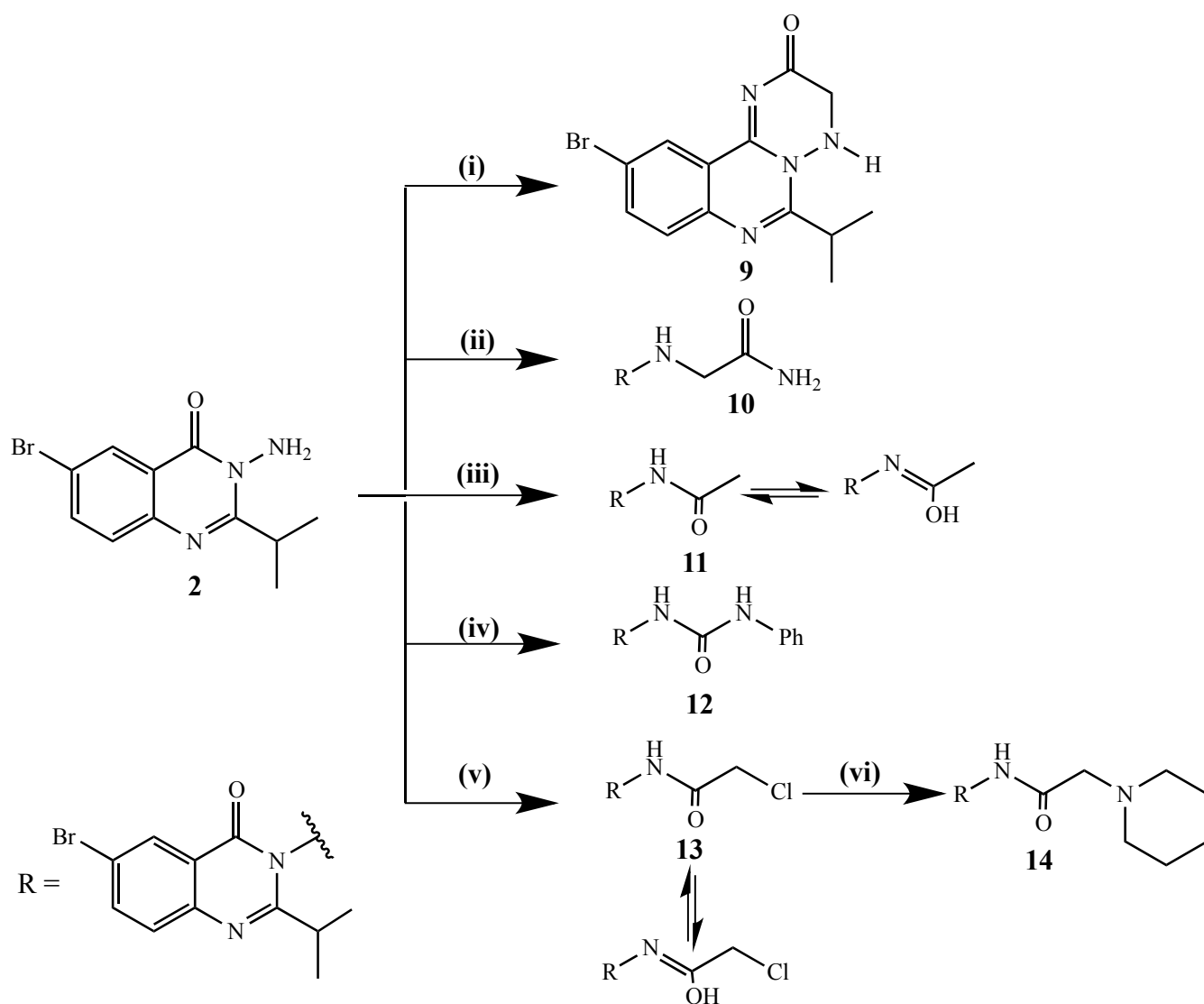


**Scheme 1. Reagents and conditions:** (i) 4-MeOC<sub>6</sub>H<sub>4</sub>CHO, EtOH, piperidine, reflux 3 h, (ii) CS<sub>2</sub>, aq. KOH, EtOH, reflux 8 h, (iii) CS<sub>2</sub>, KOH, EtOH, stirring at rt, (iv) N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O, oil bath, (170 °C) 5 h, (v) RCOCl, dry benzene, reflux 4 h, (vi) POCl<sub>3</sub>, stirring with dropwise addition for 20 min, then gradual heating to 150 °C for 10 min.

The literature prompted the authors to generate, in the present work, some chemotherapeutic agents which might have anticancer activity. Thus, 3-amino-6-bromo-2-isopropyl-4(3*H*)-quinazolin-4-one (**2**) have been utilized to construct new substances containing a quinazoline core through its reaction with chloroacetamide (under different conditions), acetic anhydride, phenyl isocyanate and ethyl chloroacetate. It has been claimed that when some 3-aminoquinazolinone derivatives were treated with chloroacetamide in DMF at refluxing temperature either for a short time (3 h),<sup>15</sup> or a long time (25 h),<sup>16</sup> a nitrogen-bridgehead product was isolated as sole product.

However, when quinazolinone **2** was allowed to react with chloroacetamide by fusion, the product was 10-bromo-6-isopropyl-3,4-dihydro[1,2,4]-triazino[2,3-*c*]quinazolin-2-one (**9**).<sup>12</sup> On the other hand, the 3-aminoquinazolinone **2** reacted with chloroacetamide in boiling *n*-butanol to give

2-(6-bromo-2-isopropyl-4-oxoquinazolin-3(4*H*)-ylamino)acetamide (**10**). The IR spectrum of **10** exhibited strong absorption bands attributable to two C=O and one NH, respectively, (Scheme 2).



**Scheme 2. Reagents and conditions:** (i)  $\text{ClCH}_2\text{CONH}_2$ , fusion,  $140^\circ\text{C}$ , 6 h (ii)  $\text{ClCH}_2\text{CONH}_2$ , *n*-BuOH, reflux 5 h, (iii)  $\text{Ac}_2\text{O}$ , AcOH, reflux 3 h, (iv) PhNCO, dry benzene, reflux 10 h, (v)  $\text{ClCH}_2\text{CO}_2\text{Et}$ , *n*-BuOH, reflux 4 h, (vi) piperidine, EtOH, reflux 6 h.

*N*-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4*H*)-yl)acetamide (**11**) was obtained on treatment of quinazolinone **2** with a mixture of acetic acid and acetic anhydride. The IR spectrum of compound **11** showed strong absorption bands attributable to C=N, two C=O group, NH, and OH, respectively. The  $^1\text{H}$  NMR spectrum of compound **11** revealed that it exists in solution in a keto-enol tautomerism of an amide functionality, as it showed two singlet signals at  $\delta$  6.63 and 8.73 attributable to NH and OH of the keto and the enol forms, respectively.

It was interesting to investigate the behavior of the aminoquinazolinone **2** towards other carbon electrophiles e.g., phenyl isocyanate in boiling benzene. Thus, when compound **2** was allowed to react

with phenyl isocyanate in boiling benzene, 1-(6-bromo-2-isopropyl-4-oxoquinazolin-3(4*H*)-yl)-3-phenylurea (**12**) was produced.<sup>17</sup> The reaction takes place *via* nucleophilic addition of the amino functionality to the isocyanate group. IR spectrum of compound **12** exhibited strong absorption bands attributable to two C=O groups and two NH groups. Also, its <sup>1</sup>H NMR spectrum showed signals at  $\delta$  9.25 and 9.63 (2s, 2H, NH, D<sub>2</sub>O-exchangeable).

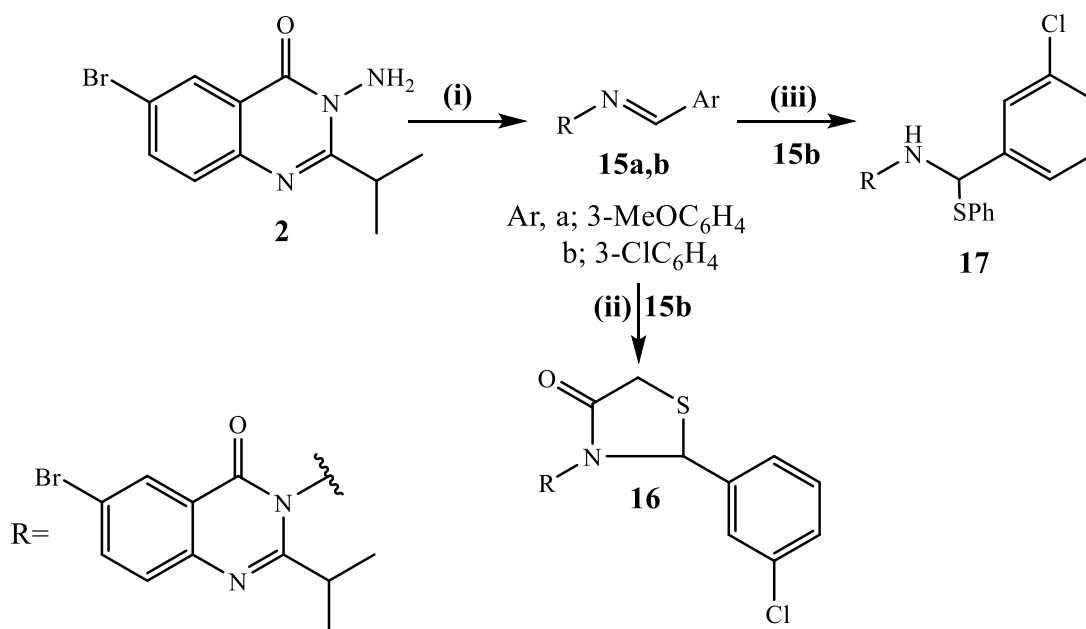
When 3-amino-4(3*H*)-quinazolinone **2** was allowed to react with other carbon electrophile namely, ethyl chloroacetate in boiling *n*-butanol, the product was identified as 1-(6-bromo-2-isopropyl-4-oxoquinazolin-3(4*H*)-yl)-2-chloroacetamide (**13**). Herein, the reaction proceeded *via* nucleophilic attack of the amino group on the ethoxycarbonyl carbon rather than the electronically deficient methylene carbon adjacent to the chlorine atom. This could be explained from the fact that reaction with ethoxycarbonyl takes place *via* a tetrahedral intermediate whereas nucleophilic displacement of chloride takes place *via* an S<sub>N</sub>2 mechanism. In the tetrahedral intermediate, the attacking amino group can bind itself completely to the carbonyl carbon before the ethoxy group begins to break off. The energy barrier that hampers the reaction is lowered when the tetrahedral intermediate proceeds, and thus, the system receives much of its "energy payment" from the formation of the new C-N bond before having to pay its "energy debt" for the breakage of the C-O bond. The structure of compound **13** was assigned from its IR spectrum which exhibited strong absorption bands attributable to two C=O and one NH, respectively and the <sup>1</sup>H NMR spectrum showed signals at  $\delta$  8.41 (s, 1H, NH, D<sub>2</sub>O-exchangeable), 8.73 (s, 1H, OH, D<sub>2</sub>O-exchangeable). It is concluded from <sup>1</sup>H NMR data that compound **13** is present in a keto-enol tautomerism of an amide functionality in a ratio of 3:2. The enol form seems to be more stable due to hydrogen bond formation.

It is interesting to investigate the behavior of compound **13** towards nitrogen nucleophiles, such as piperidine where reaction occurs *via* an S<sub>N</sub>2 mechanism. Thus, when compound **13** was allowed to react with piperidine in boiling ethanol, it afforded *N*-(6-bromo-2-isopropyl-4-oxoquinazolin-3(4*H*)-yl)-2-(piperidinyl)acetamide (**14**). The IR spectrum of **14** exhibits strong absorption bands attributable to two C=O groups and NH (hydrogen bonded and non-hydrogen bonded).

Azomethines (Schiff bases) having potential biological activities, prepared by reaction of 3-aminoquinazolinones with different aldehydes.<sup>18,19</sup> Thus, condensation of compound **2** with aromatic aldehydes, namely 3-methoxybenzaldehyde, and 3-chlorobenzaldehyde afforded 3-(arylideneamino)-6-bromo-2-isopropyl-4(3*H*)quinazolinones (**15a,b**) (Scheme 3).

The IR spectra of **15** were consistent with the assigned structure. The spectra revealed the absence of NH and the presence of bands in the region 1675-1685 and 1605-1615 cm<sup>-1</sup> and 2875-2980 cm<sup>-1</sup>, for C=O, C=N and C-H, respectively. The activated azomethine group (-N=CH) in compound **15** prompted the authors to study the behavior of compound **15** towards aliphatic and aromatic thiols.<sup>20,21</sup> Thus, when compound **15b** was submitted to react with thioglycolic acid, addition takes place initially, followed by

cyclization to give 6-bromo-3-[2-(3-chlorophenyl)-4-oxothiazolidin-3-yl]-2-isopropylquinazolin-4(3*H*)-one (**16**). The IR spectrum of compound **16** showed strong absorption bands at 692, 1670, 1697  $\text{cm}^{-1}$  attributable to C-S and two C=O groups. The spectrum lacks any band for NH.



**Scheme 3. Reagents and conditions:** (i) ArCHO, EtOH, piperidine (few drops), reflux 3 h, (ii) HSCH<sub>2</sub>CO<sub>2</sub>H, piperidine (few drops), water bath 3 h, (iii) PhSH, dry benzene, piperidine (few drops), reflux 1 h.

On the other hand, when compound **15b** was allowed to react with thiophenol in the presence of a few drops of piperidine,<sup>22</sup> 6-bromo-3-[(3-chlorophenyl)(phenylthio)methylamino]-2-isopropylquinazolin-4(3*H*)-one (**17**) was produced. The structure of compound **17** was established from the following evidence: (i) the elemental analysis indicated the presence of sulfur; (ii) the IR spectrum exhibited absorption bands attributable to C-S, C=O, and NH, respectively; (iii) the <sup>1</sup>H NMR spectrum showed signals at 4.13 (s, 1H, CH-S) and 8.83 (s, 1H, NH, D<sub>2</sub>O-exchangeable).

### **In vitro cytotoxicity assay:**

The preliminary cytotoxic study of any new molecule is ideally performed *in vitro* against a set of cell lines, and it is one of the most widely accepted techniques for anticancer screening. The *in vitro* cytotoxicity of the newly synthesized compounds was performed with the sulforhodamine B (SRB) assay according to previously described methods.<sup>23,24</sup> The cell lines used are breast cancer (MCF-7), hepatocellular carcinoma (HepG2), cervical cancer (HeLa), and human promyelocytic leukemia (HL-60). Cytotoxic activities of the tested compounds are summarized in Table 1. From the Table, it could be concluded that the synthesized target molecules were found to exhibit different cytotoxicity at concentrations between 9.8 and 4.5  $\mu\text{M}$  on the different cell lines, except compounds **3** and **15a,b** which

exhibited high cytotoxicity (approximately 50% inhibition) at concentrations between 1 and 0.5  $\mu\text{M}$ ), which means that these derivatives can be further utilized as a promising anticancer agents.

**Table 1.** *In-vitro* anticancer screening of the synthesized compounds against different cell line

Compound No	IC <sub>50</sub> $\mu\text{M}$			
	MCF-7 (breast cancer)	HepG2 (hepatocellular carcinoma)	HeLa (cervical cancer)	HL-60 (human promyelocytic leukemia)
1	7.6	7.1	7.3	8.2
2	8.3	8.5	9.7	8.2
3	0.8	1.0	0.7	0.9
4	8.5	9.7	6.1	7.5
5	8.9	7.6	8.1	8.3
6	5.8	6.5	9.8	7.4
7a	9.6	8.5	8.8	7.4
7b	9.1	9.6	8.5	8.3
8	4.2	5.8	4.9	6.2
9	6.7	6.1	5.1	5.6
10	7.5	7.2	8.4	8.1
11	7.3	6.9	7.6	6.3
12	7.2	8.7	5.9	6.8
13	5.8	6.9	4.5	6.4
14	4.9	6.2	7.5	6.6
15a	0.6	0.9	0.7	0.8
15b	0.8	0.5	1.0	0.9
16	7.6	9.5	5.0	7.2
17	8.7	6.8	7.4	9.1

## EXPERIMENTAL

All melting points are uncorrected and measured on Stuart electric melting point apparatus. Infrared (IR) spectra were recorded on Bruker 2000 spectrometer using KBr disks. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured on Varian Mercury 300 and 75 MHz spectrometer using TMS as an internal standard and CDCl<sub>3</sub> as a solvent; chemical shifts are measured in ppm. The mass spectra were recorded on a Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV using the electron ionization technique. Elemental

analysis was carried out by The Microanalytical Center, Faculty of Science, Cairo University and the microanalyses were within  $\pm 0.3\%$  of the theoretical values. The biological evaluation of the products was carried out at Biochemistry Department, Faculty of Science, Ain Shams University. 2-(6-Bromo-2-isopropylquinazolin-4-yloxy)acetylhydrazide (**1**) and 3-amino-6-bromo-2-isopropylquinazolin-4(3*H*)-one (**2**) have been prepared according to methods described in one of our recent publications.<sup>11</sup> Compounds **2** and **9** were previously prepared by Madkour.<sup>12</sup>

#### ***N'*-(4-Methoxybenzylidene)-2-(6-bromo-2-isopropylquinazolin-4-yloxy)acetylhydrazide (3).**

To a mixture of **1** (3.4 g, 10 mmol) and anisaldehyde (1.06 g, 10 mmol) in EtOH (30 mL) a few drops of piperidine was added and the reaction mixture was refluxed for 3 h. The solid that separated out after cooling and concentration was filtered off to give **3** (3.15 g, 69%); yellow crystals; mp 154-156 °C (EtOH); IR (KBr) 1608, 1684  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.36 (d,  $J = 6.60$  Hz, 6H, 2 $\text{CH}_3$ - *i*-Pr.), 3.42-3.62 (m, 1H, CH-*i*-Pr), 3.78 (s, 3H,  $\text{OCH}_3$ ), 4.86 (s, 2H, O- $\text{CH}_2$ -C=O), 6.93-8.32 (m, 8H, Ar-H and N=CH), 8.41 (s, 1H, NH,  $\text{D}_2\text{O}$ -exchangeable).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  181.0, 172.8, 170.3, 162.7, 150.5, 137.0, 130.1, 128.5, 125.9, 122.4, 119.5, 114.2, 112.9, 144.3, 69.1, 55.4, 28.9, 21.1; MS  $m/z$  456 ( $\text{M}^+$ , 55), 458 (51). Anal. Calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_4\text{O}_3\text{Br}$  (457); C, 55.14; H, 4.60; N, 12.25. Found: C, 55.32; H, 4.81; N: 12.49.

#### **5-[(6-Bromo-2-isopropylquinazolin-4-yloxy)methyl]-1,3,4-oxadiazole-2-thiol (4).**

A mixture of **1** (3.4 g, 10 mmol), and potassium hydroxide (0.56 g, 10 mmol) in EtOH (50 mL) was treated with carbon disulfide (20 mmol). The reaction mixture was refluxed for 5 h and the excess solvent was distilled off under reduced pressure. The residue was diluted with water and acidified with HCl. The solid that separated out was filtered off to give **4** (2.17 g, 57%); deep yellow crystals; mp 187-189 °C (EtOH); IR (KBr) 1243, 1590, 2515  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.32 (d, 6H,  $J = 6.73$  Hz, 2 $\text{CH}_3$ , *i*-Pr.), 3.21 (s, 1H, SH,  $\text{D}_2\text{O}$ -exchangeable), 3.40- 3.58 (m, 1H, CH-*i*-Pr), 5.41 (s, 2H, O- $\text{CH}_2$ -C=N), 7.83-8.16 (m, 3H, Ar-H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  181.1, 171.1, 169.2, 154.2, 150.4, 137.0, 128.6, 122.2, 119.3, 112.9, 71.9, 29.0, 21.2; MS  $m/z$  380 ( $\text{M}^+$ , 100), 382 ( $\text{M}+2$ , 93). Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_4\text{O}_2\text{BrS}$  (381): C, 44.09; H, 3.41; N, 14.70. Found: C, 43.87; H, 3.24; N, 14.51.

#### **Potassium 2-(2-((6-bromo-2-isopropylquinazolin-4-yl)oxy)acetyl)hydrazine-1-carbodithioate (5).**

Compound **1** (3.4 g, 10 mmol) was dissolved in an ice-cold alcoholic KOH solution (0.56 g, 10 mmol KOH in 50 mL EtOH) followed by dropwise addition of carbon disulfide (150 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure. The obtained solid was filtered off and washed by cold absolute EtOH (2x5 mL) to afford the potassium salt **5** (3.48 g, 77%) a pale yellow crystals, mp above 300 °C; IR (KBr) 1620, 1680, 3298, 3412  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (300



MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.34 (d,  $J = 6.54$  Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.18-3.33 (m, 1H, CH-*i*-Pr), 4.89 (s, 2H, O-CH<sub>2</sub>-C=O), 7.95-8.18 (m, 3H, Ar-H), 2.16 and 8.23 (2s, 2H, 2NH, D<sub>2</sub>O-exchangeable). MS  $m/z$  414 ( $M^+ - K$ , 100).

**4-Amino-5-[(6-bromo-2-isopropylquinazolin-4-yloxy)methyl]-4*H*-1,2,4-triazol-3-thiol (6).**

A suspension of **5** (50 mmol) and hydrazine hydrate (10 mmol) was heated in an oil bath at 170 °C for 5 h. The reaction mixture was left to cool, diluted with water, and neutralized with HCl. The formed precipitate was filtered off to afford **6** (2.84 g, 72%); a pale green crystals; mp 260-262 °C (EtOH); IR (KBr) 2520, 3100, 3210 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (d,  $J = 6.71$  Hz; 6H, 2CH<sub>3</sub>-*i*-Pr), 2.35 (s, 2H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 2.97-3.11 (m, 1H, CH-*i*-Pr), 5.33 (s, 2H, O-CH<sub>2</sub>-C=N), 7.79-8.39 (m, 3H, Ar-H); 11.27 (s, 1H, SH, D<sub>2</sub>O-exchangeable); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  181.0, 169.8, 166.3, 151.5, 150.2, 137.1, 128.4, 122.3, 119.4, 112.9, 66.7, 29.0, 21.3; MS  $m/z$  394 ( $M^+$ , 67), 396 ( $M+2$ , 63). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>6</sub>OBrS (395): C, 42.53; H, 3.80; N, 21.27. Found: C, 42.26; H, 3.63; N, 21.47.

**General procedure for the preparation of compounds 7a,b.**

A suspension of **1** (3.4 g, 10 mmol), and acid chloride (10 mmol) namely acetyl chloride and benzoyl chloride, in dry benzene (30 mL) was heated under reflux for 4 h. The solid that separated, after concentrating and cooling the reaction solution, was filtered off and crystallized from the proper solvent to give **7a** and / or **7b**.

***N'*-[2-(6-Bromo-2-isopropylquinazolin-4-yloxy)acetyl]acetylhydrazide (7a):** (2.55 g, 67%); white crystals; mp 195-197 °C (benzene); IR (KBr) 1610, 1680, 3100, 3171 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.23 (d,  $J = 6.59$ , Hz 6H, 2CH<sub>3</sub>-*i*-Pr), 2.41 (s, 3H, COCH<sub>3</sub>), 3.30-3.48 (m, 1H, CH-*i*-Pr), 4.66 (s, 2H, O-CH<sub>2</sub>-C=O), 7.81-8.34 (m, 3H, Ar-H), 8.77 and 8.94 (2 s, 2H, 2 NH, D<sub>2</sub>O-exchangeable), MS  $m/z$  380 ( $M^+$ , 100), 382 ( $M+2$ , 97). Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub>Br (381): C, 47.24; H, 4.46; N, 14.70. Found: C, 46.97; H, 4.21; N, 14.53.

***N'*-[2-(6-Bromo-2-isopropylquinazolin-4-yloxy)acetyl]benzohydrazide (7b):** (3.36 g, 75%); yellow crystals; mp 225-227 °C (benzene/EtOH); IR (KBr) 1620, 1687, 3123, 3200 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.21 (d,  $J = 6.84$  Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.39-3.51 (m, 1H, CH-*i*-Pr), 4.72 (s, 2H, O-CH<sub>2</sub>-C=O), 7.58-8.23 (m, 8H, Ar-H), 8.69 and 8.82 (2 s, 2H, 2 NH, D<sub>2</sub>O-exchangeable). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  181.2, 169.8, 165.9, 164.6, 150.5, 137.1, 131.9, 131.8 128.6, 128.5, 127.3 122.4, 119.5, 112.9, 68.8, 28.9, 21.1; MS  $m/z$  442 ( $M^+$ , 100), 444 ( $M+2$ , 95), Anal. Calcd for C<sub>20</sub>H<sub>19</sub>N<sub>4</sub>O<sub>3</sub>Br (443): C, 54.18; H, 4.29; N, 12.64. Found: C, 54.31; H, 4.12; N, 12.45.

**2-(((6-Bromo-2-isopropylquinazolin-4-yl)oxy)methyl)-5-phenyl-1,3,4-oxadiazole (8).**

To a stirred solution of **7b** (4.43 g, 10 mmol) phosphorous oxychloride (5 mL) was added dropwise over a period of 20 min at 0 °C. The temperature of the reaction mixture was gradually raised to 150 °C and then it was kept at this temperature for 15 min in an oil bath. The reaction solution was left to cool and poured onto ice / H<sub>2</sub>O with stirring. The solid that separated out was filtered off to give **8** (3.19 g, 75%); brown crystals; mp 230-232 °C; IR (KBr) 1612 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.24 (d, *J* = 6.90 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr.), 3.43-3.60 (m, 1H, CH-*i*-Pr), 4.96 (s, 2H, O-CH<sub>2</sub>-C=N), 7.15-8.35 (m, 8H, Ar-H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 181.2, 169.8, 164.1, 154.0, 150.5, 137.0, 128.9, 128.5, 128.3, 127.2, 122.6, 122.3, 119.6, 112.8, 72.5, 28.8, 21.1; MS *m/z* 424 (M<sup>+</sup>, 78), 426 (M+2, 76). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub>Br (425): C, 56.47; H, 4.00; N, 13.18. Found: C, 56.22; H, 3.86; N, 13.31.

**10-Bromo-6-isopropyl-3,4-dihydro[1,2,4]triazino[2,3-*c*]quinazolin-2-one (9).**<sup>12</sup> mp 167-169 (literature 164 °C); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 198.8, 163.2, 144.1, 134.0, 130.6, 124.5, 121.5, 120.8, 55.2, 27.8, 20.6; MS *m/z*, 320 (M<sup>+</sup>, 100), 322 (M+2, 98).

**2-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4*H*))ylamino)acetamide (10).**

A solution of **2** (2.82 g, 10 mmol), and chloroacetamide (0.93 g, 10 mmol) in boiling *n*-BuOH (30 mL) was heated at refluxing temperature for 5 h. After cooling, the obtained solid was filtered off to give **10** (2.14 g, 63%); white crystals; mp 294-296 °C (AcOH); IR (KBr) 1660, 1684, 3140 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.23 (d, *J* = 6.80 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 2.85-3.10 (m, 1H, CH-*i*-Pr), 3.62 (s, 2H, N-CH<sub>2</sub>-C=O), 6.72 (br s, 2H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.44-8.33 (m, 3H, Ar-H), 10.63 (s, 1H, NH, D<sub>2</sub>O-exchangeable), <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 169.6, 164.2, 160.4, 145.6, 136.0, 132.1, 124.3, 122.8, 121.5, 54.9, 27.9, 20.5; MS *m/z* 338 (M<sup>+</sup>, 100), 340 (M+2, 97). Anal. Calcd for C<sub>13</sub>H<sub>15</sub>N<sub>4</sub>O<sub>2</sub>Br (339): C, 46.02; H, 4.42; N, 16.52. Found: C, 46.29; H, 4.53; N, 16.33.

***N*-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4*H*))yl)acetamide (11).**

A solution of **2** (2.82 g, 10 mmol) and acetic anhydride (30 mmol) in glacial acetic acid (30 mL) was heated at refluxing temperature for 3 h. When the reaction mixture was left to cool and diluted with cold water, the solid which separated out was filtered off to afford **11** (2.07 g, 64%); white crystals; mp 248-250 °C (EtOH); IR (KBr), 1605, 1673, 1692, 3180, 3261, 3384, 3487 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.28 (d, *J* = 6.42 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 2.16 (s, 3H, CH<sub>3</sub>-C=O), 2.72-2.90 (m, 1H, CH-*i*-Pr), 6.63 (s, 1H, NH, D<sub>2</sub>O-exchangeable), 7.43-8.35 (m, 3H, Ar-H), 8.73 (s, 1H, OH, D<sub>2</sub>O-exchangeable). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 168.0, 163.1, 160.3, 145.6, 136.1, 132.2, 124.2, 122.8, 121.5, 27.1, 20.5, 20.1; MS *m/z* 323 (M<sup>+</sup>, 35), 325 (M+2, 33). Anal. Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub>Br (324): C, 48.15; H, 4.32; N, 12.96. Found: C, 48.32; H, 4.51; N, 13.05.

**1-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4H)-yl)-3-phenylurea (12).**

A mixture of **2** (2.82 g, 10 mmol) and phenyl isocyanate (4.76 g, 40 mmol) in dry benzene (40 mL) was heated at refluxing temperature for 10 h on a steam bath. The reaction mixture was distilled under reduced pressure, the formed solid was filtered off to afford **12** (2.89 g, 72%); white crystals; mp 220-222 °C (toluene); IR (KBr) 1653, 1715, 3292, 3320 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 6.82 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.45-3.70 (m, 1H, CH-*i*-Pr), 7.00-8.43 (m, 8H, Ar-H), 9.25 and 9.63 (2s, 2H, NH, D<sub>2</sub>O-exchangeable); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.4, 159.8, 153.6, 145.6, 139.1, 136.0, 131.9, 128.7, 127.8, 124.2, 122.8, 121.5, 121.2, 27.2, 20.5; MS *m/z* 400 (M<sup>+</sup>, 41), 402 (M+2, 38). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub>Br (401): C, 53.87; H, 4.24; N, 13.97. Found: C, 53.62; H, 4.45; N, 13.70.

**1-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4H)-yl)-2-chloroacetamide (13).**

A solution of **2** (2.82 g, 10 mmol) and ethyl chloroacetate (1.23 g, 10 mmol) in *n*-BuOH (30 mL) was heated at refluxing temperature for 4 h. The reaction mixture was concentrated under reduced pressure. After cooling, the formed solid was filtered off to afford **13** (2.33 g, 65%); pale yellow crystals; mp 155-157 °C (light petroleum 60-80 °C); IR (KBr), 1660, 1676, 3322 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.27 (d, *J* = 6.44 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.55-3.68 (m, 1H, CH-*i*-Pr), 4.19 (s, 2H, O-CH<sub>2</sub>-Cl), 6.92-7.94 (m, 3H, Ar-H), 8.41 (s, 1H, NH, D<sub>2</sub>O-exchangeable), 8.73 (s, 1H, OH, D<sub>2</sub>O-exchangeable); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.1, 163.7, 160.3, 145.7, 136.0, 132.1, 124.2, 122.8, 121.5, 40.1, 27.1, 20.5; MS *m/z* 357 (M<sup>+</sup>, 100), 359 (M+2, 92). Anal. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>BrCl (358): C, 43.58; H, 3.63; N, 11.73. Found: C, 43.34; H, 3.41; N, 11.52.

***N*-(6-Bromo-2-isopropyl-4-oxoquinazolin-3(4H)-yl)-2-(piperidinyl)acetamide (14).**

A solution of **13** (3.58 g, 10 mmol) and piperidine (0.97 g, 10 mmol) in EtOH (30 mL) was heated under reflux for 6 h, concentrated and left to cool. The solid that settled down was filtered off to give **14** (2.85 g, 70%); white crystals; mp 200-202 °C (benzene); IR (KBr) 1632, 1675, 3215, 3321 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (d, *J* = 6.92 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 1.55-1.62 (m, 6H, piperidine moiety), 2.20-2.25 (m, 4H, piperidine moiety), 3.24-3.44 (m, 1H, CH-*i*-Pr), 3.64 (s, 2H, N-CH<sub>2</sub>-C=O), 7.42-8.23 (m, 3H, Ar-H), 8.59 (s, 1H, NH, D<sub>2</sub>O-exchangeable), 8.94 (s, 1H, OH, D<sub>2</sub>O exchangeable); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.1, 163.9, 160.3, 145.6, 136.1, 132.0, 124.3, 122.8, 121.5, 58.8, 54.1, 25.3, 24.2, 27, 20.6; MS *m/z* 406 (M<sup>+</sup>, 100), 408 (M+2, 96). Anal. Calcd for C<sub>18</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Br (407): C, 53.07; H, 5.65; N, 13.76. Found: C, 53.31; H, 5.44; N, 13.52.

**3-(Arylideneamino)-6-bromo-2-isopropylquinazolin-4(3H)-one (15a,b).**

A mixture of **2** (2.82 g, 10 mmol), (10 mmol) of the appropriate aromatic aldehyde namely, 3-methoxybenzaldehyde, and 3-chlorobenzaldehyde, and few drops of piperidine, as a basic catalyst, in

EtOH (30 mL) was heated at refluxing temperature for 3 h. The solid that separated out after concentration and cooling was crystallized from the proper solvent to produce **15a,b**.

**6-Bromo-2-isopropyl-3-((3-methoxybenzylidene)amino)quinazolin-4(3H)-one (15a):** (2.72 g, 68%); yellow crystals; mp 154-156 °C (benzene); IR (KBr) 1605, 1675, 2875 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.27 (d, *J* = 6.80 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.17-3.33 (m, 1H, CH-*i*-Pr), 3.75 (s, 3H, OCH<sub>3</sub>), 7.18-8.12 (m, 7H, Ar-H), 8.28 (s, 1H, N=CH); MS *m/z* 399 (M<sup>+</sup>, 39), 401 (M+2, 36). Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub>Br (400): C, 57.00; H, 4.50; N, 10.50. Found: C, 57.28; H, 4.71; N, 10.23.

**6-Bromo-2-isopropyl-3-((3-chlorobenzylidene)amino)quinazolin-4(3H)-one (15b):** (2.91 g, 72%); white crystals, mp 170-172 °C (light petroleum 60-80 °C); IR (KBr) 1615, 1685, 2980 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 6.60 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.12-3.26 (m, 1H, CH-*i*-Pr), 7.22-8.29 (m, 7H, Ar-H), 8.32 (s, 1H, N=CH). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.9, 157.1, 153.6, 145.7, 136.3, 136.0, 132.1, 131.6, 130.4, 128.7, 124.5, 122.8, 121.5, 27.6, 20.5; MS *m/z* 403 (M<sup>+</sup>, 95), 405 (100). Anal. Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>OBrCl (404): C, 53.47; H, 3.71; N, 10.40. Found: C, 53.66; H, 3.92; N, 10.66.

**6-Bromo-3-[2-(3-chlorophenyl)-4-oxothiazolidin-3-yl]-2-isopropylquinazolin-4(3H)-one (16).**

A mixture of **15b** (4.04 g, 10 mmol) and thioglycolic acid (0.92 g, 10 mmol) in dry benzene (30 mL) was treated with few drops of piperidine, and then heated on a water bath for 3 h. The solid that separated out after cooling was filtered off and washed with light petroleum (40-60 °C) to afford **16** (3.15 g, 66%); yellow crystals; mp 124-126 °C (benzene); IR (KBr) 692, 1670, 1697 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.32 (d, *J* = 6.45 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.12-3.30 (m, 1H, CH-*i*-Pr), 3.34-3.38 and 3.45-3.49 (2d, *J*=12.00 Hz, 2H, S-CH<sub>2</sub>-C=O), 6.01 (s, 1H, CH of thiazolidinone moiety), 7.10-8.26 (m, 7H, Ar-H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 168.5, 163.7, 159.8, 145.8, 137.0, 136.1, 132.5, 132.1, 129.8, 128.5, 124.5, 122.8, 121.5, 54.9, 35.4, 27.7, 20.6; MS *m/z* 477 (M<sup>+</sup>, 64), 479 (68). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>BrClS (478): C, 50.21; H, 3.56; N, 8.79. Found: C, 50.42; H, 3.74; N, 9.02.

**6-Bromo-3-[(3-chlorophenyl)(phenylthio)methylamino]-2-isopropylquinazolin-4(3H)-one (17).**

A mixture of **15b** (4.04 g, 10 mmol) and thiophenol (1.1 g, 10 mmol) in dry benzene (30 mL) was treated with few drops of piperidine and then heated under reflux for 1 h. The solid that separated out was filtered off and washed with light petroleum (40-60 °C) to afford **17** (3.08 g, 60%); as yellow crystals, mp 220-223 °C (benzene); IR (KBr) 684, 1677, 3365 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (d, *J* = 6.92 Hz, 6H, 2CH<sub>3</sub>-*i*-Pr), 3.62-3.82 (m, 1H, CH-*i*-Pr), 4.13 (s, 1H, CH-S), 6.93-8.41 (m, 12H, Ar-H), 8.83 (s, 1H, NH, D<sub>2</sub>O-exchangeable). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.7, 160.3, 145.6, 140.2, 136.3, 136.1, 132.4, 132.0, 129.5, 129.3, 128.8, 128.6, 124.9, 124.3, 122.8, 121.5, 65.5, 27.5, 20.6. MS *m/z* 513 (M<sup>+</sup>,

100), 515 (96). Anal. Calcd for  $C_{24}H_{21}N_3OBrClS$  (514): C, 56.03; H, 4.09; N, 8.17. Found: C, 56.26; H, 4.33; N, 8.39.

### Experimental for cytotoxicity assay

Preliminary anticancer experiments were done as follows:

- 1) Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the tested compounds to allow the attachment of cells to the wall of the plate.
- 2) Exponentially growing cells were collected using 0.25% Trypsin-EDTA
- 3) Cells were exposed to the drugs for 72 h and subsequently fixed with TCA (10%) for 1 h at 4 °C.
- 4) After several washings, cells was exposed to 0.4% SRB solution for 10 min in a dark place and subsequently washed with 1% glacial acetic acid.
- 5) After drying overnight, Tris-HCl was used to dissolve the SRB-stained cells and the color intensity was measured at 540 nm.<sup>24</sup>
- 6) The experiments were performed in duplicate.  $IC_{50}$  was defined as the drug concentration required to reduce optical density to 50% of that of the control (i.e.,  $K_d = IC_{50}$  when  $R = 0$  and  $E_{max} = 100 - R$ ).<sup>25</sup>

### ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to Prof. Dr. Fatma Farag, Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt, for her efforts in performing the *in vitro* cytotoxicity.

### REFERENCES

1. P. Ballard, R. Bradbury, C. Harris, L. Hennequin, M. Hickinson, J. Kettle, J. Kendrew, T. Klinowska, D. Ogilvie, S. Pearson, E. Williams, and I. Wilson, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4908.
2. M. Ranson, *Br. J. Cancer*, 2004, **90**, 2250.
3. D. Fabbro, S. Ruetz, E. Buchdunger, S. W. Cowan-Jacob, G. Fendrich, J. Liebetanz, J. Mestan, T. O'Reilly, P. Traxler, B. Chaudhuri, H. Fretz, J. Zimmermann, T. Meyer, G. Carvatti, P. Furet, and P.W. Manley, *Pharmacol. Ther.*, 2002, **93**, 79.
4. M. N. Noolvi and H. M. Patel, *Lett. Drug Des. Discov.*, 2010, **7**, 556.
5. M. N. Noolvi, H. M. Patel, and V. Bhardwaj, *Med. Chem.*, 2011, **7**, 200.
6. M. N. Noolvi, H. M. Patel, and V. Bhardwaj, *Dig. J. Nanomater. Bios.*, 2010, **5**, 387.
7. M. N. Noolvi, H. M. Patel, V. Bhardwaj, and A. Chauhan, *Eur. J. Med. Chem.*, 2011, **46**, 2327.

8. S. T. Al-Rashood, I. A. Aboldahab, M. N. Nagi, L. A. Abouzeid, A. A. M. Abdel-Aziz, S. G. Abdel-Hamide, K. M. Yousef, A. M. Al-Obaid, and H. I. El-Subbagh, [Bioorg. Med. Chem., 2006, 14, 8608.](#)
9. A. M. Al-Obaid, S. G. Abdel-Hamide, H. A. El-Kashef, A. A. M. Abdel-Aziz, A. S. El-Azab, H. A. Al-Khamees, and H. I. El-Subbagh, [Eur. J. Med. Chem., 2009, 44, 2379.](#)
10. F. A. M. Al-Omary, L. A. Abouzeid, M. N. Nagi, E. E. Habib, A. A. M. Abdel-Aziz, A. S. El-Azab, S. G. Abdel-Hamide, M. A. Al-Omar, A. M. Al-Obaid, and H. I. El-Subbagh, [Bioorg. Med. Chem., 2010, 18, 2849.](#)
11. M. A. El-Hashash, M. E. Azab, and J. M. Morsy, [J. Heterocycl. Chem., \(in press\) 2015. DOI 10.1002/jhet.2389.](#)
12. H. M. F. Madkour, *ARKIVOC*, 2004, **i**, 36.
13. H. A. Saad, N. A. Osman, and A. H. Moustafa, [Molecules, 2011, 16, 10187.](#)
14. A. M. Alafeefy, A. A. Kadi, O. A. Al-Deeb, K. E. H. El-Tahir, and N. A. Al-Jaber, [Eur. J. Med. Chem., 2010, 45, 4947.](#)
15. R. El-Sayed and A. F. Wasfy, [J. Chin. Chem. Soc., 2005, 52, 129-.](#)
16. R. R. Dangi, N. Hussain, A. Josh, G. Pemawat, and G. L. Talesara, *Ind. J. Chem.*, 2011, **50B**, 1165.
17. M. S. Amin, M. A. El-Hashash, and I. A. Attia, *Ind. J. Chem.*, 1993, **32B**, 577.
18. A. J. Atia and S. S. Al-Mufrgeiy, [Am. J. Chem., 2012, 2, 150.](#)
19. G. Saravanan, P. Pannerselvan, and C. R. Prakash, *Der Pharmacia Lett.*, 2010, **2**, 216.
20. A. Kumar and C. S. Rajput, [Eur. J. Med. Chem., 2009, 44, 83.](#)
21. A. M. Alafeefy, A. S. El-Azab, M. A. Mohamed, M. A. Bakhat, and S. G. Abdel-Hamid, *J. Saudi Chem. Soc.*, 2011, **15**, 319.
22. M. A. El-Hahash, F. M. Soliman, M. S. Amine, and M. Morsi, *Phosphorous, Sulfur Silicon Relat. Elem.*, 1992, **69**, 299.
23. P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, and M. R. Boyd, [J. Natl. Cancer Inst., 1990, 1107.](#)
24. A. B. Abdel-Naim, A. A. Nagy, A. M. Mohamadin, H. M. El-Mazar, and A. E. Ahmed, [Toxicol. Lett., 2009, 190, 123.](#)
25. A. M. Al-Abd, J. H. Lee, S. Y. Kim, N. Kun, and H. J. Kuh, [Cancer Sci., 2008, 99, 423.](#)