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## SYNTHESIS AND HETEROCYCLIZATIONS OF 3,4-DIHYDROQUINAZOLIN-2-YL GUANIDINE IN THE SEARCH OF NEW ANTICANCER AGENTS<sup>1</sup>

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**Abstract** – The cyclocondensations of 3,4-dihydroquinazolin-2-yl guanidine with a variety of electrophilic reagents *viz.* aldehydes, ketones, triethyl orthoformate, diethyl ethoxymethylenemalonate, carbon disulfide and trichloroacetonitrile were found to afford 1,3,5-triazino[2,1-*b*]quinazolines. However, some unexpected reactions were also observed. The structural properties such as tautomerism and hinderance to conformational rotation were also investigated. The results of biological testing suggested that the 1,3,5-triazino[2,1-*b*]quinazoline nucleus could be a new promising scaffold for the development of potential anticancer agents.

### INTRODUCTION

In our previous studies<sup>2</sup> we found that the heterocyclization of benzimidazol-2-yl guanidines (**1**) with one-carbon inserting reagents afforded 1,3,5-triazino[1,2-*a*]benzimidazoles, particularly 2-amino-4,4-dimethyl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazole (**2**) (Fig. 1), which was able to inhibit one of the key enzymes in cellular methabolism, namely dihydrofolate reductase (DHFR).

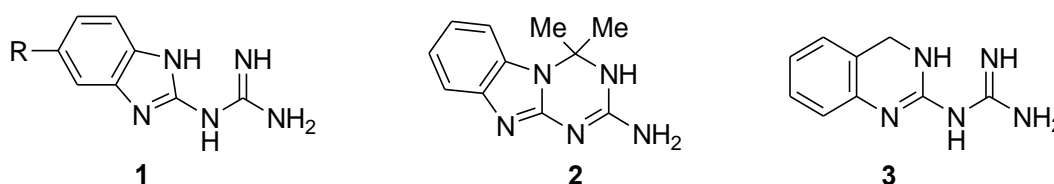


Figure 1

In order to extend this methodology to the synthesis of structurally similar 1,3,5-triazinoquinazolines with potential anticancer activity, we report here the preparation of 3,4-dihydroquinazolin-2-yl guanidine (**3**) (Fig. 1) and its reactions with a variety of electrophiles.

Information on the synthesis of 1,3,5-triazinoquinazolines is limited. In general, three isomeric structures are possible for quinazoline fused with 1,3,5-triazine nucleus, *viz.* 1,3,5-triazino[1,2-*a*]quinazoline (**A**),<sup>3</sup> 1,3,5-triazino[2,1-*b*]quinazoline (**B**)<sup>4</sup> and 1,3,5-triazino[1,2-*c*]quinazoline (**C**)<sup>4a,5</sup> heterocyclic systems (Fig. 2). The cyclization of 3,4-dihydroquinazolin-2-yl guanidine (**3**) might hypothetically result in the formation of systems **A** or **B**. In previous study, we also found that cyclization of unsymmetrically substituted in the phenylene fragment benzimidazol-2-yl guanidines (**1**, R ≠ H) with one-carbon inserting reagents did not proceed regioselectively.<sup>2a</sup> Therefore, regioselectivity of the ring closure of **3** became one of the important aspects of our investigation. With regards to DHFR inhibitory activity of **2**<sup>2</sup> and antiproliferative properties of other structurally related fused 1,3,5-triazines synthesized in our laboratory<sup>6</sup>, we also report herein the results of the biological testing for the compounds prepared.

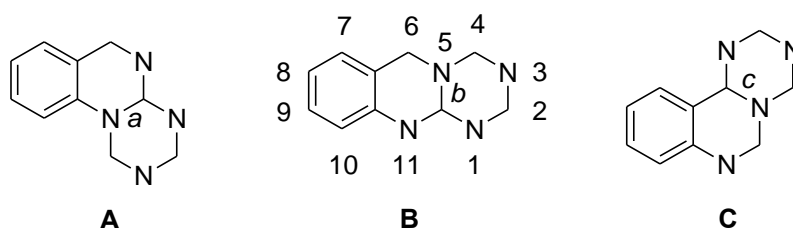
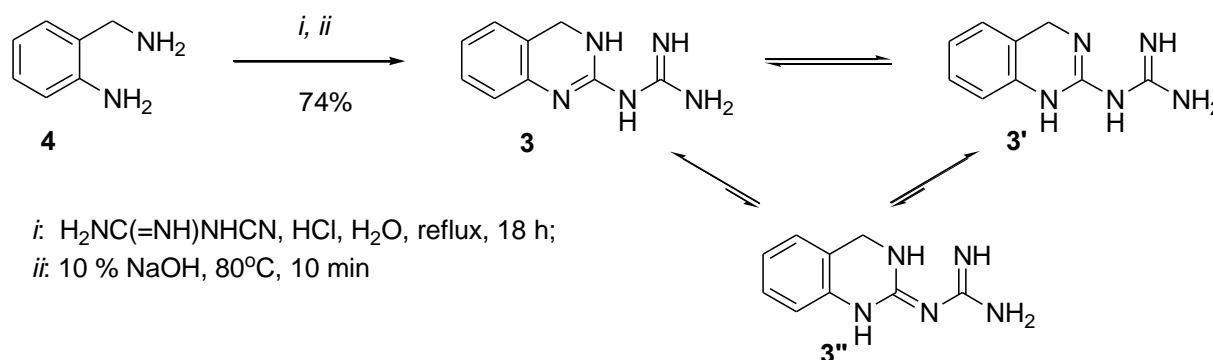


Figure 2

## RESULTS AND DISCUSSION

### Synthesis

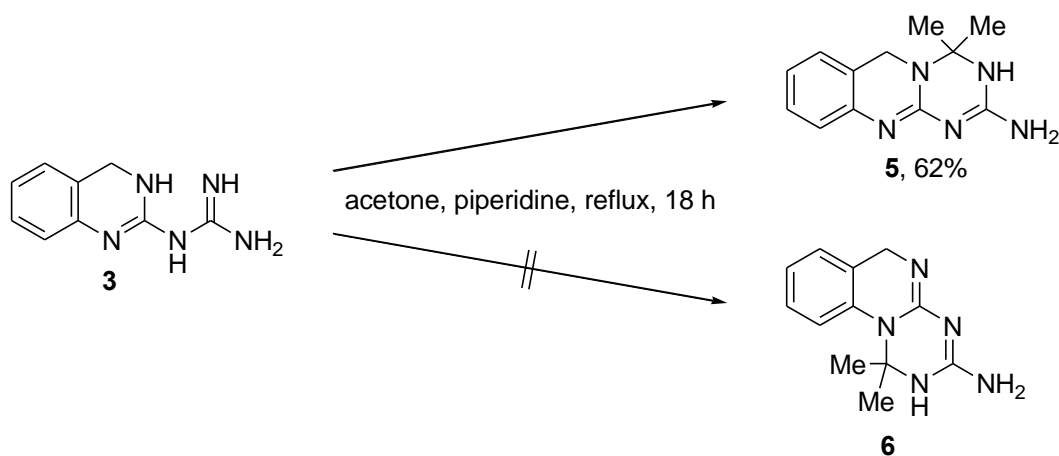
3,4-Dihydroquinazolin-2-yl guanidine (**3**) was prepared using acid catalyzed cyclocondensation of 2-aminobenzylamine (**4**) and cyanoguanidine (Scheme 1).



Scheme 1

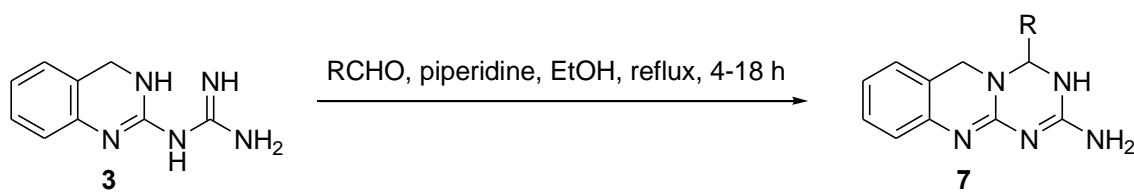
Broadening of the signals of C-2, C-4, C-8 and C-8a atoms observed in  $^{13}\text{C}$  NMR spectrum of **3** indicated the existence of dihydroquinazolin-2-yl guanidine in equilibrium of two forms **3** and **3'** due to annular tautomerism. The presence of tautomeric form **3''** in the equilibrium was less probable as no broadening for the signal of the guanidine group carbon atom in the  $^{13}\text{C}$  NMR spectrum was detected.

In our attempt to prepare an analogue of bioactive compound **2**, 3,4-dihydroquinazolin-2-yl guanidine (**3**) was heated in acetone under piperidine catalysis. The 1,3,5-triazine ring closure reaction resulted in the formation of product with two geminal methyl groups for which two alternative structures **5** and **6** could be attributed (Scheme 2). The formation of the dihydro-1,3,5-triazine ring with  $sp^3$  hybridized quaternary carbon atom was confirmed by the presence of signals at 71.2 ppm in  $^{13}\text{C}$  NMR spectrum. 2D NOESY experiments showed cross-peaks between the singlets of the *gem*-dimethyl groups and the methylenic protons of dihydroquinazoline nucleus indicating their close proximity. These observations confirmed the annelation of the triazine ring to side *b* of quinazoline and led to the assignment of the 2-amino-4,4-dimethyl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazoline (**5**) structure for the reaction product.



Scheme 2

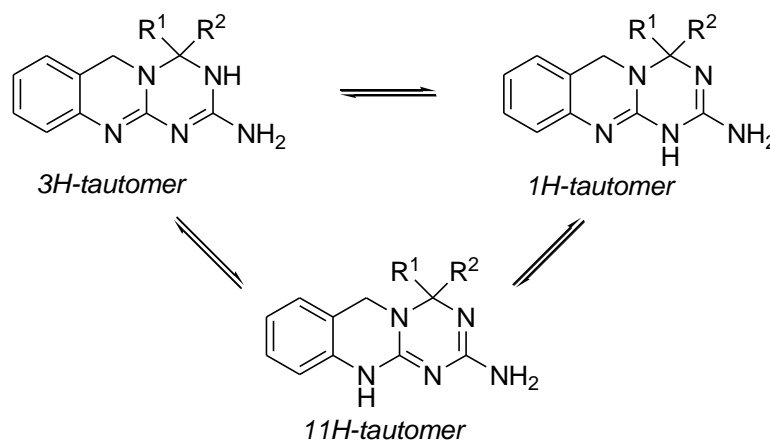
The reaction of 3,4-dihydroquinazolin-2-yl guanidine (**3**) with (het)arylaldehydes proceeded *via* (5+1) heterocyclization with the formation of 2-amino-4-(het)aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolines (**7**) (Scheme 3). The reaction was found to be general and regioselective. The signal of the  $sp^3$ -hybridized carbon atom at 70-74 ppm in the  $^{13}\text{C}$  NMR spectra indicated the ring closure with the formation of dihydro-1,3,5-triazine nucleus. Another evidence of the cyclization was a coupling ( $J_{\text{gem}} \approx 14.5$  Hz) of the signals of methylenic protons of the dihydroquinazoline ring in  $^1\text{H}$  NMR spectra of the products **7**. These protons became diastereotopic and their signals appeared as two doublets of AM system at 3.90-4.20 and 4.25-4.40 ppm. The dihydro-1,3,5-triazine ring fusion on side *b* of the quinazoline was confirmed by cross-peaks found in 2D NOESY experiments for the signals of methylenic protons and the singlet of proton at newly introduced  $sp^3$ -hybridized carbon of the nucleus.



Compound	R	Yield, %	Compound	R	Yield, %
<b>7a</b>	Ph	85	<b>7e</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	58
<b>7b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	84	<b>7f</b>	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	75
<b>7c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	87	<b>7g</b>	2-Thienyl	82
<b>7d</b>	4-MeC <sub>6</sub> H <sub>4</sub>	72	<b>7h</b>	3-Py	77

Scheme 3

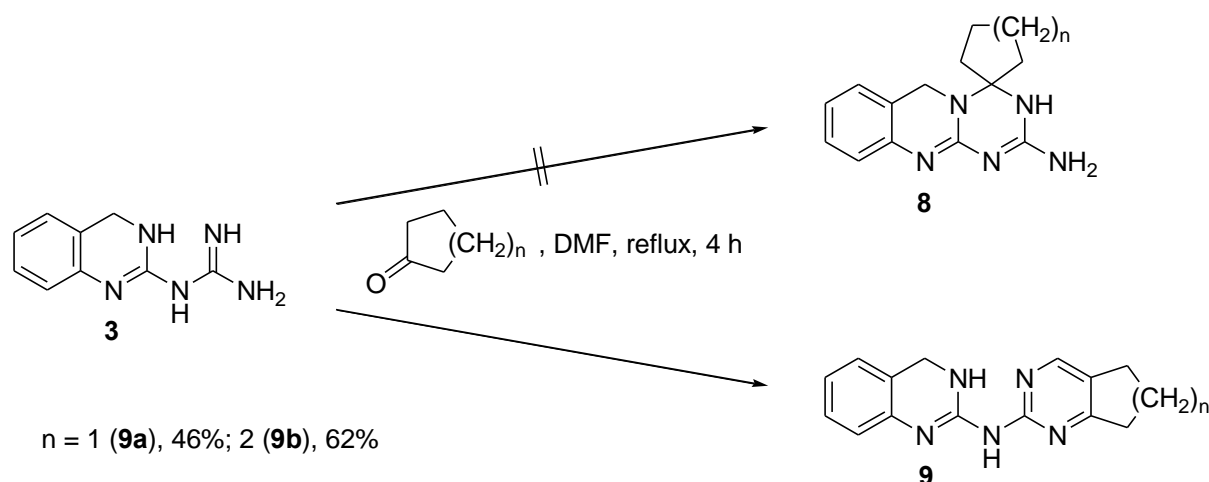
The annular prototropic tautomerism was noticed in DMSO solution for compounds **5** and **7** viz. *1H*-, *3H*- and *11H*-tautomeric forms (Scheme 4). The prototropic interconversion between these tautomeric forms was postulated based on broadening observed for several signals of 4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazoline heterocyclic system in the <sup>13</sup>C NMR spectra of compounds **5** and **7**. The pattern of the signal broadening indicated that all three tautomeric forms were involved in the proton transfer. The broadening of C-4 signal referred to the *1H*- / *3H*-equilibrium and the broad signals of C-10a and C-10 indicated the *1H*- / *11H*-interconversion.



Scheme 4

Heating cycloketones (e.g. cyclopentanone and cyclohexanone) with benzimidazol-2-yl guanidine (**1**, R = H) in DMF has been shown to provide spiro-fused 1,3,5-triazines.<sup>2b,7</sup> When similar conditions were applied for the reaction of **3** with these ketones, the formation of fused 1,3,5-triazines (**8**) with similar structure was expected (Scheme 5). However, instead of dihydrotriazine ring closure, the reaction furnished the formation of compounds **9** with pyrimidine ring constructed from guanidine moiety, two

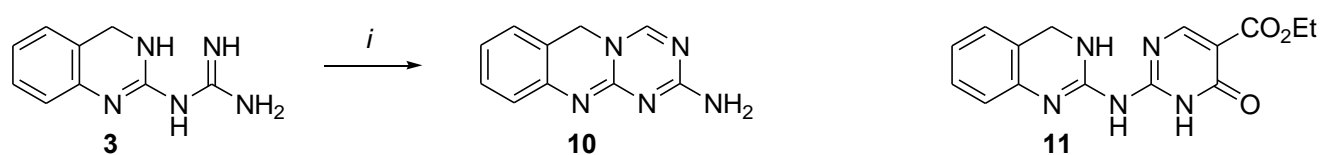
carbon atoms of cycloketone and one molecule of DMF, which was also involved in the reaction.



Scheme 5

Orthoesters are well known as one-carbon inserting reagents in heterocyclic chemistry for a long time.<sup>8</sup> The reaction of **3** with triethyl orthoformate proceeded regioselectively with the 1,3,5-triazine ring closure onto side *b* of the dihydroquinazoline affording 2-amino-6*H*-1,3,5-triazino[2,1-*b*]quinazoline (**10**) (Scheme 6). This was confirmed by the observation of cross-peaks between the signals of methylenic protons of quinazoline and methine proton of triazine ring in 2D NOESY experiment. <sup>1</sup>H NMR spectrum of **10** showed two separate D<sub>2</sub>O exchangeable signals at 7.20 and 7.24 ppm corresponding to the amino group. The magnetic unequivalence of the amino group protons can be explained on the basis of strong  $\pi$ -electrons delocalization of the amino group with the 1,3,5-triazine ring<sup>9</sup> that resulted in increasing rotational barrier. The activation energy ( $\Delta G^\ddagger_{308}$ ) for the rotation around C-NH<sub>2</sub> bond was found to be 70.6 kJ/mol as estimated by dynamic NMR experiments.

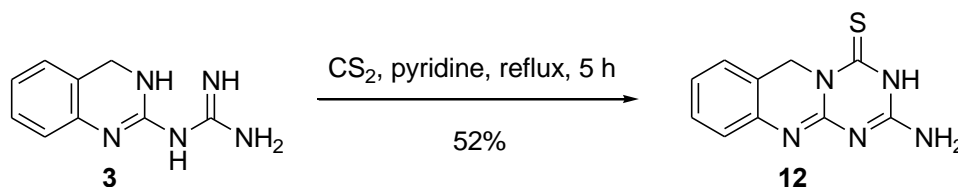
Diethyl ethoxymethylenemalonate as a potential triatomic synthon<sup>10</sup> might theoretically react with guanidine moiety providing **11** (Scheme 6). However, likewise in the reaction with benzimidazol-2-yl guanidines (**1**),<sup>2</sup> diethyl ethoxymethylenemalonate reacted with **3** playing a role of one-carbon inserting reagent affording the formation of **10**. The reaction proceeded with elimination of ethanol and diethyl malonate and afforded the product (**10**) identical to the one obtained from the reaction of **3** with triethyl orthoformate.



*i*:  $\text{HC}(\text{OEt})_3$ , DMF, reflux, 4 h (Method A), 63%;  $\text{EtOCH}=\text{C}(\text{CO}_2\text{Et})_2$ , MeCN, reflux, 7 h (Method B), 82%

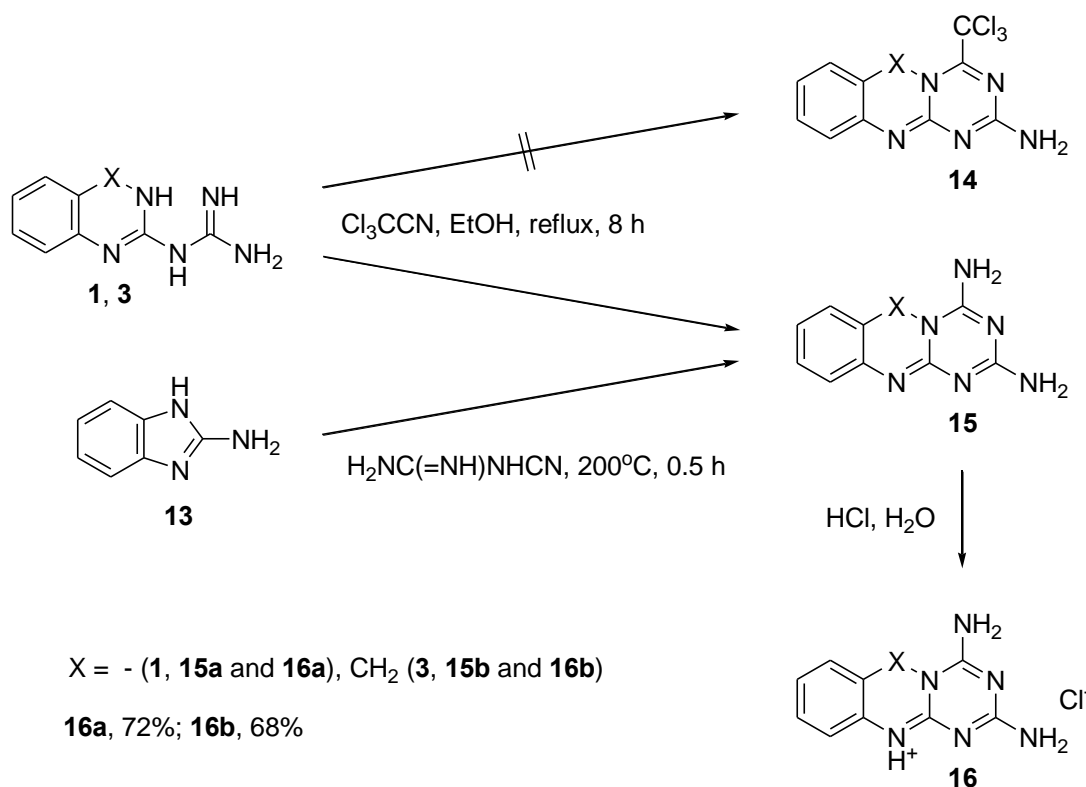
Scheme 6

Carbon disulfide has been recognized as valuable reagent in organic chemistry, particularly useful for thiocarbonylation reactions.<sup>11</sup> The ring closure thiocarbonylation of **3** with carbon disulfide was successfully achieved (Scheme 7) using the method described by Martin *et al.*<sup>7</sup> for structurally related benzimidazol-2-yl guanidine (**1**, R = H). The structure of the product (**12**) was confirmed by spectroscopic data. The presence of the thioxo group at C-4 was supported with a significant stretching absorption at  $1186\text{ cm}^{-1}$  in the IR spectrum of compound **12** and signal at 182.8 ppm in the  $^{13}\text{C}$  NMR spectrum for this atom. The anisotropic effect of the thioxo group caused a downfield shift of the signal of methylenic protons (5.40 ppm) in  $^1\text{H}$  NMR spectrum, thus indicating the formation of the 1,3,5-triazine ring onto side *b* of quinazoline.



Scheme 7

Trichloroacetonitrile has been known as a useful synthon in heterocyclic chemistry,<sup>12</sup> particularly it has found an application as one-carbon inserting reagent for the construction of 1,3,5-triazine ring introducing trichloromethyl or amino group.<sup>13</sup> We found that **3** reacted with trichloroacetonitrile in ethanol with elimination of chloroform, therefore providing the formation of diamine **15b** (Scheme 8).



Scheme 8

Similarly, benzimidazol-2-yl guanidine (**1**) under the same reaction conditions provided 2,4-diamino-1,3,5-triazino[1,2-*a*]benzimidazole (**15a**), which was identical to the compound prepared *via* alternative synthetic pathway from 2-aminobenzimidazole (**13**) and cyanoguanidine according to the method reported by Kreutzberger and Tantawy.<sup>14</sup> The reactions of trichloroacetonitrile with heterylguanidines (**1** and **3**) in ethanol were found to proceed chemo- and regioselectively affording with good yields **15**, exclusively; no traces of possible alternative product **14** were detected. Therefore, trichloroacetonitrile could be considered as a safer replacement of cyanogen bromide used in this type of reactions.<sup>7</sup>

Due to solubility problem, compounds **15** were converted into their hydrochloric salts. In both cases, the protonation occurred at endocyclic nitrogen atom not belonging to the triazine ring that was confirmed by 2D NOESY experiment data (cross-peaks between signals of N<sup>+</sup>H and phenylene proton). Additionally, for compound **16b**, the cross-peaks observed between the singlet of methylenic protons at 5.12 ppm and the signals of one of the amino groups at 7.76-7.78 ppm confirmed the regiochemistry of the triazine ring closure to side *b* of quinazoline nucleus. The same cross-peaks also facilitated the assignments of signals of the amino groups for this compound.

The hindered rotation was detected for the amino groups of **16**. The activation energy ( $\Delta G^\ddagger$ ) of the rotation around C(2)-NH<sub>2</sub> bond was estimated for compounds **16** using dynamic <sup>1</sup>H NMR spectroscopy. For 2,4-diamino-1,3,5-triazino[1,2-*a*]benzimidazole hydrochloride (**16a**), the value of  $\Delta G^\ddagger_{333}$  was equal 71.4 kJ/mol; for 2,4-diamino-6*H*-1,3,5-triazino[2,1-*b*]quinazoline (**10**),  $\Delta G^\ddagger_{320}$  was found to be 73.6 kJ/mol.

### Biological activity

The antiproliferative activity of the prepared 1,3,5-triazino[2,1-*b*]quinazolines against lung (A549) and breast (MDA-MB-231) cancer cell lines was evaluated using MTT assay.<sup>15</sup> 4-(Het)aryl substituted 2-amino-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolines (**7**) were the only group of compounds which possessed antiproliferative activity in micromolar range (Table 1). This is the first time, anticancer activity was reported for compounds with 1,3,5-triazino[2,1-*b*]quinazoline scaffold. The antiproliferative activity of the compounds (**7**) seemed to depend on their lipophilicity. The more lipophilic halogen substituted **7b** and **7c** showed higher antiproliferative effect.

In the enzyme assay, no significant effect on the human DHFR activity was observed in the presence of the compounds at 100  $\mu$ M. Therefore, the effect of the compounds on the growth of cancer cells was not associated with DHFR inhibition.

### CONCLUSION

New 1,3,5-triazino[2,1-*b*]quinazolines were effectively prepared *via* cyclocondensation of 3,4-dihydroquinazolin-2-yl guanidine (**3**) with variety of one-carbon inserting reagents. The reactions

were found to be chemo- and regioselective. The 1,3,5-triazino[2,1-*b*]quinazoline nucleus was identified as a new scaffold for the development of potential anticancer agents.

Table 1. *Antiproliferative activity of some 2-amino-4-(het)aryl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-*b*]quinazolines (7)*

Compound	R	GI <sub>50</sub> , μM	
		MDA-MB-231	A549
<b>7a</b>	Ph	93	110
<b>7b</b>	4-ClC <sub>6</sub> H <sub>4</sub>	27	33
<b>7c</b>	4-BrC <sub>6</sub> H <sub>4</sub>	17	15
<b>7d</b>	4-MeC <sub>6</sub> H <sub>4</sub>	61	33
<b>7e</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	98	40
<b>7f</b>	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	53	27
<b>7g</b>	2-Thienyl	92	104
<b>7h</b>	3-Py	> 100	> 100

## EXPERIMENTAL

**General Methods.** Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. The IR spectra were recorded with a Shimadzu IRPrestige-21 spectrophotometer using KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-*d*<sub>6</sub> as a solvent and TMS as an internal reference. The dynamic NMR experiments were performed using 0.5 M solutions of the compounds in DMSO-*d*<sub>6</sub>.

### *1(3),4-Dihydroquinazolin-2-yl guanidine (3).*

2-Aminobenzylamine (**4**, 5.0 g, 41 mmol) and cyanoguanidine (4.3 g, 51 mmol) were dissolved in 15 mL of water with 8 mL of conc. HCl. The mixture was refluxed for 18 h, cooled and filtered. The hydrochloride salt of **3** was dissolved in water on heating and the resulting solution was filtered hot and basified with 5% NaOH solution. After stirring for 10 min and cooling, the precipitate was filtered and washed with water. The product (**3**) was purified by reprecipitation from the hot solution in 5% HCl using 5% NaOH. The analytical sample was recrystallized from EtOH. Yield 74%; mp 198 °C (lit.,<sup>16</sup> mp 202-204 °C).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 4.32 (2H, s, C(4)H<sub>2</sub>), 5.93 (1H, br s, NH), 6.67 (1H, d, *J* = 7.9 Hz, H-8), 6.72 (1H, t, *J* = 7.5 Hz, H-6), 6.94 (4H, br s, NHC(=NH)NH<sub>2</sub>), 7.01 (1H, d, *J* = 7.2 Hz, H-5), 7.05 (1H, t, *J* = 7.5 Hz, H-7).



$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  42.8 (br s, C-4), 120.3 (C-8), 120.6 (C-4a), 121.1 (br s, C-8), 125.0 (C-6), 127.0 (C-7), 145.3 (br s, C-8a), 159.5 (NHC(=NH)NH<sub>2</sub>), 159.9 (br s, C-2).

**2-Amino-4,4-dimethyl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (5).**

To suspension of 3,4-dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) in acetone (10 mL), piperidine (0.2 mL) was added. The reaction mixture was heated under reflux for 18 h. After cooling, the product (**5**) was filtered and recrystallized from a mixture of acetone and EtOH. Yield 62%; mp 246 °C.

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.37 (6H, s, 2Me), 4.45 (2H, s, C(6)H<sub>2</sub>), 6.35 (2H, br s, NH<sub>2</sub>), 6.77 (1H, d,  $J = 7.9$  Hz, H-10), 6.81 (1H, t,  $J = 7.5$  Hz, H-8), 7.01 (1H, d,  $J = 7.9$  Hz, H-7), 7.05 (1H, t,  $J = 7.5$  Hz, H-9).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  27.0 (2Me), 42.7 (C-6), 71.2 (br s, C-4), 117.1 (br s, C-10), 119.7 (C-6a), 120.8 (C-8), 125.4 (C-9), 127.6 (C-7), 140.4 (br s, C-10a), 151.5 (C-2), 153.4 (br s, C-11a).

Anal. Calcd for C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.75; H, 6.68; N, 30.37.

**General Procedure for Synthesis of 2-Amino-4-(het)aryl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolines (7).** To solution of 3,4-dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) in EtOH (7 mL), appropriate aldehyde (2.5 mmol) and piperidine (0.2 mL) were added. After heating under reflux for 4-18 h, the reaction mixture was cooled. The product (**7**) was filtered and recrystallized from a suitable solvent.

**2-Amino-4-phenyl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7a).**

Yield 85%; mp 219-220 °C (EtOH).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  3.97 (1H, d,  $J_{gem} = 14.3$  Hz, H<sub>A</sub>-6), 4.34 (1H, d,  $J_{gem} = 14.3$  Hz, H<sub>M</sub>-6), 5.50 (1H, s, H-4), 6.09 (2H, br s, NH<sub>2</sub>), 6.79 (1H, t,  $J = 7.3$  Hz, H-8), 6.82 (1H, d,  $J = 7.3$  Hz, H-10), 6.90 (1H, d,  $J = 7.3$  Hz, H-7), 7.06 (1H, t,  $J = 7.3$  Hz, H-9), 7.23-7.46 (5H, m, Ph).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  45.8 (C-6), 74.0 (br s, C-4), 117.0 (br s, C-10), 118.7 (C-6a), 121.3 (C-8), 125.5 (C-9), 126.4 (C-2' and C-6'), 127.8, 127.9 (C-7 and C-4'), 128.5 (C-3' and C-5'), 139.3 (br s, C-10a), 142.6 (C-1'), 151.3 (C-2), 153.9 (br s, C-11a).

Anal. Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.02; H, 5.62; N, 25.03.

**2-Amino-4-(4-chlorophenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7b).**

Yield 84%; mp 156 °C (EtOH).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  3.95 (1H, d,  $J_{gem} = 14.3$  Hz, H<sub>A</sub>-6), 4.33 (1H, d,  $J_{gem} = 14.3$  Hz, H<sub>M</sub>-6), 5.53 (1H, s, H-4), 5.59 (2H, br s, NH<sub>2</sub>), 6.81 (1H, t,  $J = 7.2$  Hz, H-8), 6.83 (1H, d,  $J = 7.5$  Hz, H-10), 6.94 (1H, d,  $J = 7.2$  Hz, H-7), 7.09 (1H, t,  $J = 7.3$  Hz, H-9), 7.38 (2H, d,  $J = 8.3$  Hz, H-2' and H-6'), 7.43 (2H, d,  $J = 8.3$  Hz, H-3' and H-5'), 9.51 (1H, br s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  45.6 (C-6), 74.1 (br s, C-4), 116.1 (br s, C-10), 118.3 (C-6a), 121.3 (C-8), 125.6 (C-9), 127.9 (C-7), 128.2 (C-2' and C-6'), 128.4 (C-3' and C-5'), 132.2 (C-4'), 138.2 (br s, C-10a), 142.0 (br s, C-1'), 151.3 (C-2), 154.4 (br s, C-11a).

Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_5\text{Cl}$ : C, 61.64; H, 4.53; N, 22.46. Found: C, 61.52; H, 4.63; N, 22.35.

**2-Amino-4-(4-bromophenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7c).**

Yield 87%; mp 164 °C (EtOH).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  3.95 (1H, d,  $J_{gem} = 14.7$  Hz,  $\text{H}_A$ -6), 4.33 (1H, d,  $J_{gem} = 14.7$  Hz,  $\text{H}_M$ -6), 5.51 (1H, s, H-4), 5.68 (2H, br s,  $\text{NH}_2$ ), 6.80 (1H, t,  $J = 7.3$  Hz, H-8), 6.83 (1H, d,  $J = 7.9$  Hz, H-10), 6.93 (1H, d,  $J = 7.2$  Hz, H-7), 7.08 (1H, t,  $J = 7.5$  Hz, H-9), 7.32 (2H, d,  $J = 8.3$  Hz, H-2' and H-6'), 7.57 (2H, d,  $J = 8.3$  Hz, H-3' and H-5'), 9.55 (1H, br s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  45.7 (C-6), 74.0 (br s, C-4), 116.3 (br s, C-10), 118.4 (C-6a), 120.8 (C-4'), 121.3 (C-8), 125.6 (C-9), 127.9 (C-7), 128.6 (C-2' and C-6'), 131.3 (C-3' and C-5'), 138.4 (br s, C-10a), 142.4 (br s, C-1'), 151.3 (C-2), 154.3 (br s, C-11a).

Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_5\text{Br}$ : C, 53.95; H, 3.96; N, 19.66. Found: C, 53.77; H, 3.98; N, 19.54.

**2-Amino-4-(4-methylphenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7d).**

Yield 72%; mp 179-180 °C (MeOH).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  2.28 (3H, s, Me), 3.94 (1H, d,  $J_{gem} = 14.3$  Hz,  $\text{H}_A$ -6), 4.30 (1H, d,  $J_{gem} = 14.3$  Hz,  $\text{H}_M$ -6), 5.44 (1H, s, H-4), 5.68 (2H, br s,  $\text{NH}_2$ ), 6.78 (1H, t,  $J = 7.3$  Hz, H-8), 6.80 (1H, d,  $J = 7.9$  Hz, H-10), 6.90 (1H, d,  $J = 7.2$  Hz, H-7), 7.06 (1H, t,  $J = 7.5$  Hz, H-9), 7.17 (2H, d,  $J = 7.9$  Hz, H-3' and H-5'), 7.25 (2H, d,  $J = 7.9$  Hz, H-2' and H-6'), 9.38 (1H, br s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  20.6 (Me), 45.6 (C-6), 74.2 (br s, C-4), 116.6 (br s, C-10), 118.6 (C-6a), 121.2 (C-8), 125.5 (C-9), 126.3 (C-2' and C-6'), 127.8 (C-7), 128.9 (C-3' and C-5'), 137.0 (C-4'), 138.9 (br s, C-10a), 139.9 (br s, C-1'), 151.3 (C-2), 153.9 (br s, C-11a).

Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_5$ : C, 70.08; H, 5.88; N, 24.04. Found: C, 69.89; H, 5.95; N, 23.86.

**2-Amino-4-(4-methoxyphenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7e).**

Yield 58%; mp 215-216 °C (AcOEt).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  3.73 (3H, s, OMe), 3.95 (1H, d,  $J_{gem} = 14.3$  Hz,  $\text{H}_A$ -6), 4.31 (1H, d,  $J_{gem} = 14.3$  Hz,  $\text{H}_M$ -6), 5.42 (1H, s, H-4), 6.23 (2H, br s,  $\text{NH}_2$ ), 6.77 (1H, t,  $J = 8.3$  Hz, H-8), 6.78 (1H, d,  $J = 8.3$  Hz, H-10), 6.88 (1H, d,  $J = 7.5$  Hz, H-7), 6.93 (2H, d,  $J = 8.3$  Hz, H-3' and H-5'), 7.04 (1H, t,  $J = 7.3$  Hz, H-9), 7.31 (2H, d,  $J = 8.3$  Hz, H-2' and H-6'), 9.35 (1H, br s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  45.8 (C-6), 55.0 (OMe), 73.4 (br s, C-4), 113.8 (C-3' and C-5'), 117.4 (br s, C-10), 118.9 (C-6a), 121.2 (C-8), 125.4 (C-9), 127.7 (C-2' and C-6'), 127.8 (C-7), 134.6 (br s,

C-1'), (br s, C-10), 118.9 (C-6a), 121.2 (C-8), 125.4 (C-9), 127.7 (C-2' and C-6'), 127.8 (C-7), 134.6 (br s, C-1'), 140.0 (br s, C-10a), 151.2 (br s, C-2), 153.6 (br s, C-11a), 159.0 (C-4').

Anal. Calcd for C<sub>17</sub>H<sub>17</sub>N<sub>5</sub>O: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.25; H, 5.82; N, 22.53.

**2-Amino-4-[4-(N,N-dimethylamino)phenyl]-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7f).**

Yield 75%; mp 212-214 °C (EtOH).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 2.87 (6H, s, NMe<sub>2</sub>), 3.96 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>A</sub>-6), 4.27 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>M</sub>-6), 5.32 (1H, s, H-4), 6.22 (2H, br s, NH<sub>2</sub>), 6.70 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 6.75 (1H, t, *J* = 7.9 Hz, H-8), 6.76 (1H, d, *J* = 7.9 Hz, H-10), 6.86 (1H, d, *J* = 7.2 Hz, H-7), 7.03 (1H, t, *J* = 7.3 Hz, H-9), 7.19 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 9.37 (1H, br s, NH).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 40.0 (NMe<sub>2</sub>), 45.7 (C-6), 73.5 (br s, C-4), 112.1 (C-3' and C-5'), 117.5 (br s, C-10), 119.0 (C-6a), 121.0 (C-8), 125.3 (C-9), 127.3 (C-2' and C-6'), 127.7 (C-7), 129.7 (br s, C-1'), 141.0 (br s, C-10a), 150.2 (C-4'), 151.3 (br s, C-2), 153.5 (br s, C-11a).

Anal. Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>: C, 67.48; H, 6.29; N, 26.23. Found: C, 67.12; H, 6.49; N, 25.82.

**2-Amino-4-(2-thienyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7g).**

Yield 82%; mp 214-215 °C (EtOH).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 4.17 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>A</sub>-6), 4.40 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>M</sub>-6), 5.81 (1H, s, H-4), 5.91 (2H, br s, NH<sub>2</sub>), 6.82 (1H, t, *J* = 7.2 Hz, H-8), 6.83 (1H, d, *J* = 7.5 Hz, H-10), 6.95 (1H, dd, *J* = 4.7, 3.7 Hz, H-4'), 6.98 (1H, d, *J* = 7.2 Hz, H-7), 7.08 (1H, t, *J* = 7.3 Hz, H-9), 7.10 (1H, d, *J* = 3.7 Hz, H-3'), 7.43 (1H, d, *J* = 4.7 Hz, H-5'), 9.62 (1H, br s, NH).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 45.6 (C-6), 70.1 (br s, C-4), 116.2 (br s, C-10), 118.7 (C-6a), 121.4 (C-8), 124.8 (C-3'), 125.5, 125.6 (C-9 and C-5'), 126.1 (C-4'), 127.9 (C-7), 138.4 (br s, C-10a), 147.5 (br s, C-2'), 150.9 (C-2), 155.0 (br s, C-11a).

Anal. Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>5</sub>S: C, 59.34; H, 4.62; N, 24.72. Found: C, 59.09; H, 4.86; N, 24.57.

**2-Amino-4-(3-pyridyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazoline (7h).**

Yield 77%; mp 215-217 °C (EtOH).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 4.00 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>A</sub>-6), 4.38 (1H, d, *J*<sub>gem</sub> = 14.3 Hz, H<sub>M</sub>-6), 5.62 (1H, s, H-4), 5.68 (2H, br s, NH<sub>2</sub>), 6.82 (1H, t, *J* = 7.3 Hz, H-8), 6.85 (1H, d, *J* = 7.2 Hz, H-10), 6.95 (1H, d, *J* = 7.5 Hz, H-7), 7.10 (1H, t, *J* = 7.5 Hz, H-9), 7.40 (1H, dd, *J* = 7.7, 4.7 Hz, H-5'), 7.74 (1H, dd, *J* = 7.5, 1.9 Hz, H-4'), 8.52 (1H, dd, *J* = 4.7, 1.5 Hz, H-6'), 8.57 (1H, d, *J* = 1.5 Hz, H-2'), 9.63 (1H, br s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  45.7 (C-6), 72.8 (br s, C-4), 116.1 (br s, C-10), 118.4 (C-6a), 121.4 (C-8), 123.8 (C-5'), 125.6 (C-9), 127.9 (C-7), 133.9 (C-4'), 138.1 (br s, C-10a), 138.2 (C-3'), 147.9 (C-2'), 149.1 (C-6'), 151.4 (C-2), 154.7 (C-11a).

Anal. Calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_6$ : C, 64.73; H, 5.07; N, 30.20. Found: C, 64.46; H, 5.43; N, 30.04.

### Reaction of 3,4-dihydroquinazolin-2-yl guanidine (**3**) with cycloketones in DMF

To solution of 3,4-dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) in DMF (5 mL), appropriate cycloketone (5.0 mmol) was added. After heating under reflux for 4 h, the reaction mixture was cooled and evaporated to half of the volume. The product (**9**) was filtered and recrystallized from a suitable solvent.

#### *N*-(6,7-Dihydro-5H-cyclopenta[d]pyrimidin-2-yl)-3,4-dihydroquinazolin-2-amine (**9a**).

Yield 46%; mp > 300 °C (DMF).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  2.01 (2H, quintet,  $J = 7.5$  Hz, C(6')H<sub>2</sub>), 2.74-2.86 (4H, m, C(5')H<sub>2</sub> and C(7')H<sub>2</sub>), 4.52 (2H, s, C(6)H<sub>2</sub>), 6.89 (1H, t,  $J = 7.0$  Hz, H-6), 6.90 (1H, d,  $J = 7.2$  Hz, H-8), 7.08 (1H, d,  $J = 7.5$  Hz, H-5), 7.13 (1H, t,  $J = 7.5$  Hz, H-7), 8.28 (1H, s, H-4'), 9.86 (2H, br s, 2NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  22.3 (C-6), 27.1 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 41.6 (C(6)H<sub>2</sub>), 115.0 (C-8), 118.6 (C-6a), 121.4 (C-6), 124.5 (C-4a'), 125.5 (C-7), 127.7 (C-5), 137.7 (C-8a), 151.3 (C-4'), 152.9 (C-2), 164.1 (C-7a'), 174.8 (C-2').

Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_5$ : C, 67.90; H, 5.70; N, 26.40. Found: C, 67.67; H, 5.96; N, 26.15.

#### *N*-(5,6,7,8-Tetrahydroquinazolin-2-yl)-3,4-dihydroquinazolin-2-amine (**9b**).

Yield 62%; mp 227 °C (EtOH).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.60-1.88 (4H, m, C(6')H<sub>2</sub> and C(7')H<sub>2</sub>), 2.58 (2H, t,  $J = 6.0$  Hz, C(5')H<sub>2</sub>), 2.69 (2H, t,  $J = 6.0$  Hz, C(8')H<sub>2</sub>), 4.51 (2H, s, C(6)H<sub>2</sub>), 6.88 (1H, d,  $J = 7.5$  Hz, H-8), 6.89 (1H, t,  $J = 7.2$  Hz, H-6), 7.08 (1H, d,  $J = 7.5$  Hz, H-5), 7.13 (1H, t,  $J = 7.5$  Hz, H-7), 8.18 (1H, s, H-4'), 9.80 (2H, br s, 2NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  21.9 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 41.6 (C(6)H<sub>2</sub>), 114.9 (C-8), 118.6 (C-6a), 120.1 (C-4a'), 121.4 (C-6), 125.6 (C-7), 127.7 (C-5), 137.7 (C-8a), 152.9 (C-2), 157.2 (C-4'), 163.0 (C-8a'), 164.5 (C-2').

Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{N}_5$ : C, 68.79; H, 6.13; N, 25.07. Found: C, 68.52; H, 6.28; N, 24.82.

#### *2*-Amino-6H-[1,3,5]triazino[2,1-*b*]quinazoline (**10**).

*Method A.* A solution of 3,4-dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) and triethyl orthoformate (0.5 mL, 3 mmol) in DMF (5 mL) was heated under reflux for 4 h. After cooling, the yellow precipitate was filtered, washed with EtOH and recrystallized from DMF.

*Method B.* A mixture of 3,4-dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) and diethyl ethoxymethylenemalonate (0.5 mL, 2.5 mmol) in MeCN (10 mL) was heated under reflux for 7 h. After cooling, precipitated product was filtered, washed with EtOH and recrystallized from DMF to provide compound identical to the sample obtained in Method A.

Yield 63% (Method A), 82% (Method B); mp 294-295 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 4.99 (2H, s, C(6)H<sub>2</sub>), 6.80 (1H, d, *J* = 7.9 Hz, H-10), 6.85 (1H, t, *J* = 7.5 Hz, H-8), 6.98 (1H, d, *J* = 7.2 Hz, H-7), 7.08 (1H, t, *J* = 7.5 Hz, H-9), 7.20 (1H, s, NH), 7.24 (1H, s, NH), 7.97 (1H, s, H-4).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 47.9 (C-6), 119.1 (C-6a), 121.7 (C-10), 122.6 (C-8), 124.9 (C-9), 128.0 (C-7), 143.9 (C-10a), 148.1 (C-2), 157.3 (C-4), 162.6 (C-11a).

Anal. Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>5</sub>: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.23; H, 4.58; N, 35.10.

#### **2-Amino-6H-[1,3,5]triazino[2,1-b]quinazolin-4-thione (12).**

3,4-Dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) and carbon disulphide (1.0 mL, 16 mmol) were added to pyridine (4.0 mL) and refluxed for 5 h. After cooling, the product was filtered, washed with MeOH and recrystallized from DMF. Yield 52%; mp > 300 °C.

IR (KBr, v, cm<sup>-1</sup>): NH 3470, NH 3267, NH 3171, CH<sub>Ar</sub> 3080, 1636, 1607, 1578, 1541, 1508, 1479, 1450, 1406, 1337, 1246, C=S 1186, 1111, 982, 820, 768, 758, 451.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 5.40 (2H, s, C(6)H<sub>2</sub>), 7.00 (1H, d, *J* = 7.9 Hz, H-10), 7.02 (1H, t, *J* = 7.5 Hz, H-8), 7.18 (1H, s, NH), 7.22 (1H, t, *J* = 7.9 Hz, H-9), 7.25 (1H, d, *J* = 7.5 Hz, H-7), 7.46 (1H, s, NH), 10.65 (1H, s, NH).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 47.9 (C-6), 114.3 (C-10), 117.8 (C-6a), 123.2 (C-8), 126.3 (C-9), 128.3 (C-7), 133.8 (C-10a), 152.7 (C-2), 160.4 (C-11a), 182.8 (C-4).

Anal. Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>5</sub>S: C, 51.93; H, 3.92; N, 30.28. Found: C, 51.71; H, 3.98; N, 30.09.

#### **2,4-Diamino[1,3,5]triazino[1,2-a]benzimidazole hydrochloride (16a).**

Benzimidazol-2-yl guanidine (**1**, 0.44 g, 2.5 mmol) and trichloroacetonitrile (0.35 mL, 3.5 mmol) was added to EtOH (7 mL) and refluxed for 8 h. After cooling, the product (**15a**) was filtered and resuspended in aqueous HCl (0.5 M, 5 mL). The solid was dissolved on heating and the resulting solution was filtered hot. After cooling, the hydrochloride salt (**16a**) was filtered and recrystallized from water. Yield 72%; mp > 300 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.40 (1H, t, *J* = 7.3 Hz, H-7), 7.48-7.59 (2H, m, H-8, and H-9), 7.98 (1H, s, NH), 8.11 (1H, s, NH), 8.63 (1H, d, *J* = 7.3 Hz, H-6), 8.63 (2H, br s, NH), 13.83 (1H, s, NH<sup>+</sup>).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 111.9 (C-6), 114.0 (C-9), 122.7 (C-7), 124.0 (C-8), 126.6 (C-5a), 129.9 (C-9a), 151.6, 151.9 (C-2 and C-10a), 162.9 (C-4).

Anal. Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>6</sub>Cl: C, 45.68; H, 3.83; N, 35.51. Found: C, 45.53; H, 4.00; N, 35.28.

**6H-[1,3,5]Triazino[2,1-b]quinazolin-2,4-diamine hydrochloride (16b).**

3,4-Dihydroquinazolin-2-yl guanidine (**3**, 0.47 g, 2.5 mmol) and trichloroacetonitrile (0.35 mL, 3.5 mmol) was added to EtOH (7 mL) and refluxed for 8 h. After cooling, the product (**15b**) was filtered and resuspended in EtOH (5 mL) and aqueous HCl (1.0 M, 2.5 mL). The solid was dissolved on heating and the resulting solution was filtered hot. After cooling, the hydrochloride salt (**16b**) was filtered and recrystallized from water. Yield 68%; mp > 300 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 5.12 (2H, s, C(6)H<sub>2</sub>), 7.04-7.17 (3H, m, H-7, H-8 and H-10), 7.21-7.32 (1H, m, H-9), 7.76 (1H, s, NH), 7.78 (1H, s, NH), 8.38 (1H, br s, NH), 8.49 (1H, br s, NH), 11.21 (1H, s, NH<sup>+</sup>).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 45.3 (C-6), 115.1 (C-10), 116.1 (C-6a), 123.7 (C-8), 125.7 (C-9), 128.7 (C-7), 132.6 (C-10a), 151.4 (C-2), 156.3 (C-4), 163.1 (C-11a).

Anal. Calcd for C<sub>10</sub>H<sub>11</sub>N<sub>6</sub>Cl: C, 47.91; H, 4.42; N, 33.52. Found: C, 47.74; H, 4.56; N, 33.38.

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## REFERENCES

1. Part 14 in the series "Fused heterocyclic systems with *s*-triazine ring", for part 13 see A. V. Dolzhenko, N. Sachdeva, G. K. Tan, L. L. Koh, and W. K. Chui, *Acta Cryst.*, 2009, **E65**, o684.
2. (a) A. V. Dolzhenko and W. K. Chui, *J. Heterocycl. Chem.*, 2006, **43**, 95; (b) A. V. Dolzhenko and W. K. Chui, *Pharm. Chem. J.*, 2007, **41**, 470.
3. (a) M. Sawada, Y. Furukawa, Y. Takai, and T. Hanafusa, *Heterocycles*, 1984, **22**, 501; (b) H. Tietz, O. Rademacher, and G. Zahn, *Eur. J. Org. Chem.*, 2000, 2105; (c) A. Kamal and P. B. Sattur, *Synthesis*, 1985, 892.
4. (a) J. T. Shaw and J. Ballentine, *J. Chem. Soc., D. Chem. Commun.*, 1969, 1040; (b) J. T. Shaw, D. M. Taylor, F. J. Corbett, and J. D. Ballentine, *J. Heterocycl. Chem.*, 1972, **9**, 125; (c) R. A. E. Winter and T. J. Villani, *US Pat. 3887554*, 1975 (*Chem. Abstr.*, **83**, 147505); (d) H. Balli, S. Gunzenhauser, I. J. Fletcher, and D. Bedekovic, *DE Pat. 3314195*, 1983 (*Chem. Abstr.*, **100**, 87256); (e) A. V. Dolzhenko, A. V. Dolzhenko, and W. K. Chui, *J. Heterocycl. Chem.*, 2008, **45**, 173.
5. (a) M. F. Abdel-Megeed and A. Teniou, *Collect. Czech. Chem. Commun.*, 1988, **53**, 329; (b) A. A. M. Aly, *J. Chem. Res.*, 2006, 461; (c) A. A. Aly, *Z. Naturforsch.*, 2006, **61B**, 1012.

6. A. V. Dolzhenko, B. J. Tan, A. V. Dolzhenko, G. N. C. Chiu, and W. K. Chui, [\*J. Fluorine Chem.\*, 2008, \*\*129\*\*, 429.](#)
7. D. Martin, H. Graubaum, G. Kempter, and W. Ehrlichmann, [\*J. Prakt. Chem.\*, 1981, \*\*323\*\*, 303.](#)
8. (a) V. V. Mezheritskii, E. P. Olekhovich, and G. N. Dorofeenko, *Usp. Khim.*, 1973, **42**, 896; (b) S. Ghosh and U. R. Ghatak, *Proc. Indian Acad. Sci., Chem. Sci.*, 1988, **100**, 235.
9. M. I. Fernandez, J. M. Oliva, X. L. Armesto, M. L. Canle, and J. A. Santaballa, [\*Chem. Phys. Lett.\*, 2006, \*\*426\*\*, 290.](#)
10. A. Kaczor and D. Matosiuk, [\*Curr. Org. Chem.\*, 2005, \*\*9\*\*, 1237.](#)
11. (a) S. Braverman, M. Cherkinsky, and M. L. Birsa, *Sci. Synth.*, 2005, **18**, 65; (b) W. D. Rudolf, [\*J. Sulfur Chem.\*, 2007, \*\*28\*\*, 295.](#)
12. (a) G. A. Shvekhgeimer, *Khim. Geterotsykl. Soedin.*, 1993, 1443; (b) S. M. Sherif and A. W. Erian, [\*Heterocycles\*, 1996, \*\*43\*\*, 1083.](#)
13. A. V. Dolzhenko, G. Pastorin, A. V. Dolzhenko, and W. K. Chui, [\*Tetrahedron Lett.\*, 2008, \*\*49\*\*, 7180.](#)
14. A. Kreuzberger and A. Tantawy, [\*Chem. Ber.\*, 1978, \*\*111\*\*, 3007.](#)
15. M. C. Alley, D. A. Scudiero, A. Monks, M. L. Hursey, M. J. Czerwinski, D. L. Fine, B. J. Abbott, J. G. Mayo, R. H. Shoemaker, and M. R. Boyd, *Cancer Res.*, 1988, **48**, 589.
16. L. Doub, L. M. Richardson, and A. Campbell, *DE Pat. 1139124*, 1962 (*Chem. Abstr.*, **58**, 53355).