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Practical synthesis of regioisomeric 5(7)-amino-6,7(4,5)-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines☆

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Abstract—A convenient and efficient synthesis of new 5-azapurine derivatives was developed. The regioisomeric 5-amino-6,7-dihydro- and 7-amino-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines were prepared in 3–4 steps from benzhydrazide via complementary and regiospecific routes as a part of our lead finding program. The molecular structures and tautomeric preferences of the compounds obtained were investigated using NMR spectral data and X-ray crystallography.

1. Introduction

Dihydrofolate reductase (DHFR) plays an essential role in cellular biochemistry and has been a well-recognized drug target for half a century. Antifolate drugs have been developed as anticancer, antibacterial, antifungal, and antiparasitic agents.[2] 4,6-Diamino-1,2-dihydro-1,3,5-triazines (e.g., antimalarial drug cycloguanil and WR 99210) are known to be potent inhibitors of DHFR.[2a,b] Recently, dihydro-1,3,5-triazino[1,2-*a*]benzimidazoles (**1**) (Fig. 1) have also been found to possess antifolate activity.[3] Reports on other examples of fused dihydro-1,3,5-triazine with DHFR inhibitory activity are limited.

As a continuation to our investigation on fused 1,3,5-triazines as potential inhibitors of DHFR,[3a,4] we became interested in the aza-analogues of the purine system that carries a bridge nitrogen, particularly the 1,2,4-triazolo[1,5-*a*]-[1,3,5]triazines (5-azapurines).[1] The 1,2,4-triazolo[1,5-*a*]-[1,3,5]triazine derivatives have been shown to possess a wide range of biological activities.[5] However, antifolate activity of the compounds with this heterocyclic scaffold has not been investigated.

There are some common structural features, which are unique to the triazine antifolates: (1) one of the carbon atoms of triazine ring should be in sp^3 hybridization (*gem*-dimethyl substitution is usually preferred); (2) the other two carbon atoms ought to be connected with nitrogen atoms of amino group or fused ring; (3) lypophilic aromatic moiety is required at the distal part of molecule. In this report we describe new practical synthesis of derivatives of 5-azapurine system, viz.

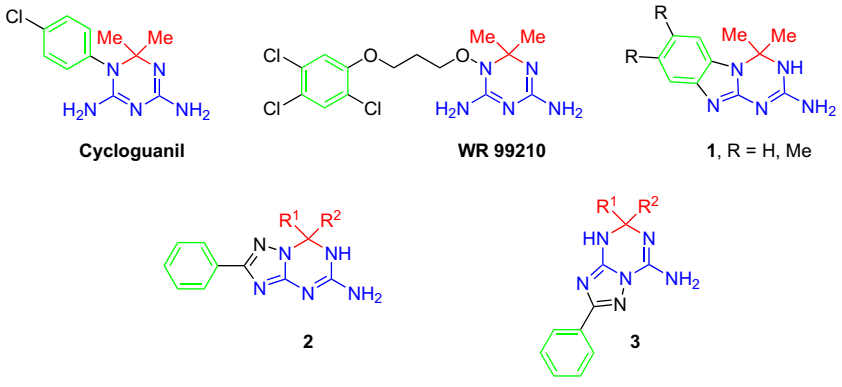

Figure 1. Selected antifolate 1,3,5-triazines and the compounds of interest.

☆ Part 8 in the series 'Fused heterocyclic systems with *s*-triazine ring', for part 7 see Ref. 1.
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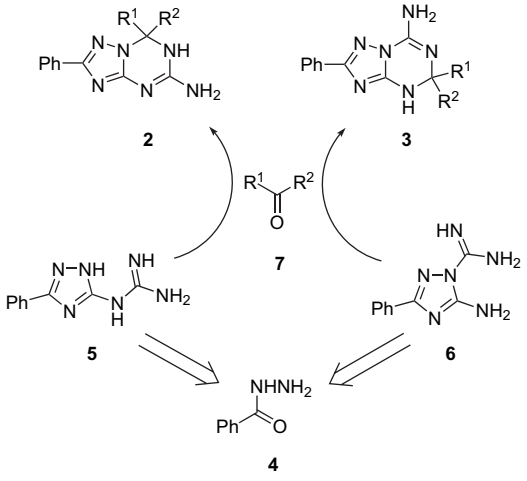
hitherto unknown regioisomeric 5-amino-6,7-dihydro- and 7-amino-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2** and **3**). These compounds contain in the structure pharmacophoric fragments (Fig. 1) of the triazine DHFR inhibitors and potentially may interact with this enzyme.

We designed a 3–4 step synthesis of dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines **2** and **3** from benzhydrazide (**4**) with the subsequent formation of the 1,2,4-triazole and the 1,3,5-triazine rings using simple procedures, inexpensive and readily available reagents that make this synthetic approach very practical. The final step that leads to the annulation of the 1,3,5-triazine nucleus, can be successfully achieved via cyclization of the suitably substituted 1,2,4-triazoles, i.e., 5-guanidino-3-phenyl-1,2,4-triazole (**5**) and 5-amino-1-guanyl-3-phenyl-1,2,4-triazole (**6**) with aldehydes or ketones **7** to generate the libraries for biological screening (Scheme 1).

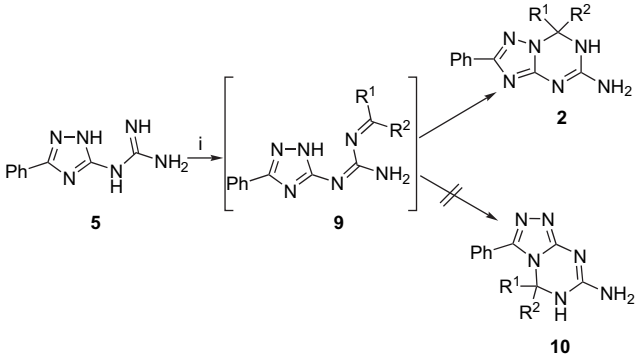


Scheme 1. Design of the 5(7)-amino-6,7(4,5)-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazines synthesis.

2. Results and discussion

The reactions of benzhydrazide (**4**) with cyanoguanidine in the presence of hydrochloric acid gave *N*-benzamidobiguanide (**8**) (Scheme 2). The treatment of *N*-benzamidobiguanide (**8**) with aqueous alkali resulted in 1,2,4-triazole ring closure and provided 5-guanidino-1,2,4-triazole **5**.

The heating of 5-guanidino-1,2,4-triazole **5** with carbonyl compounds **7** in ethanol in the presence of piperidine gave 5-amino-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines **2** (Scheme 3, Table 1). This heterocyclization was found to proceed smoothly with a variety of aldehydes and ketones. The reaction was regioselective and afforded only the products of the ring closure to nitrogen atom N-1 of the triazole **5**; the products of the ring closure to nitrogen atom N-4 (compounds **10**) as well as possible intermediates **9** were not isolated. The signal of sp^3-hybridized carbon atom in ^{13}C NMR spectra at 62–80 ppm indicated that the triazine ring closure had occurred. The formation of theoretically possible regioisomeric structure **10** was excluded based on 2D NOESY experiments (no cross-peaks were found between R^1 or R^2 and phenyl group) and X-ray crystallography of compound **2h** (Fig. 2).[6]



Scheme 3. Reagents and conditions: (i) **7a–g** (1 equiv) or **7i,j** (2 equiv), EtOH, piperidine (0.4 equiv), 3–24 h, reflux (72–96%); for **2h** acetone, piperidine (0.4 equiv), 18 h, reflux (98%).

Table 1. 5-Amino-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2**)

2	R^1	R^2	Yield (%)
a	H	Ph	92
b	H	4-MeO–C_6H_4	91
c	H	4-Me–C_6H_4	90
d	H	4-Cl–C_6H_4	73
e	H	4-F–C_6H_4	76
f	H	2-Furyl	72
g	H	4-Py	78
h	Me	Me	98
i		–$(CH_2)_4$–	96
j		–$(CH_2)_5$–	72

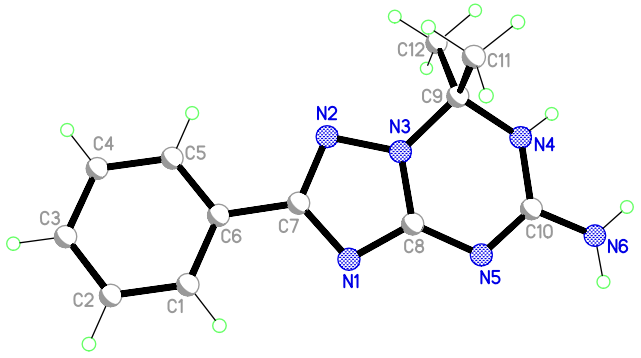
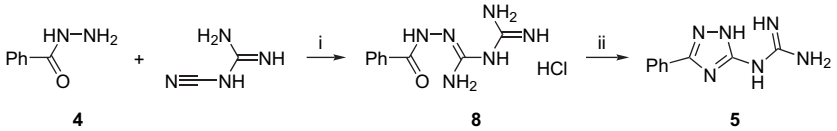
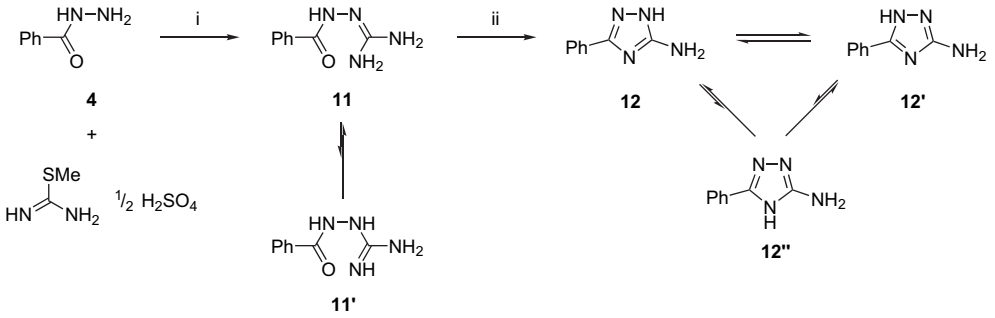


Figure 2. X-ray crystal structure of **2h**.

The synthesis of the regioisomeric 7-amino-4,5-dihydro-[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**3**) was also initiated from benzhydrazide (**4**). The reactions of **4** with *S*-methyl isothiourea gave *N*′-benzamidoguanidine (**11**) (Scheme 4). The



Scheme 2. Reagents and conditions: (i) cyanoguanidine (1.1 equiv), HCl (1 equiv), EtOH, 4 h, reflux (80%); (ii) 10% NaOH, 6 h, 80 °C (68%).



Scheme 4. Reagents and conditions: (i) *S*-methylisothiouronium sulfate (0.5 equiv), NaOH (1 equiv), H_2O, 72 h, rt, 3 h, 50 °C (86%); (ii) H_2O, 4 h, reflux (97%).

two signals of NH_2 groups in ^1H NMR spectra of the compound **11** indicated that tautomeric form **11**, rather than form **11′**, was preferred in DMSO solution ($\Delta G^{\ddagger}_{316}$ = 67.6 kJ). *N*-Benzamidoguanidine (**11**) was found to be stable: it could be recrystallized from water or aqueous ethanol and no changes were observed after drying at 140 °C under vacuum for 24 h.

In general, *N*-benzamidoguanidine (**11**) could be cyclized to aminotriazoles with elimination of water molecule. The reported methods[7] required heating of **11** to above its mp (220 °C) or refluxing with sodium ethoxide. We found that the ring closure could be achieved easier and with higher yield. When *N*-benzamidoguanidine (**11**) was heated in water, the triazole **12** was obtained in almost quantitative yield (Scheme 4). The reaction was found to be clean and afforded **12** with excellent purity. ^1H NMR spectroscopy studies of the 1,2,4-triazoles **12** in DMSO solution concluded that 5-amino-3-phenyl-1,2,4-triazole (**12**) was predominant in the equilibrium, while 3-amino-5-phenyl-1,2,4-triazole (**12′**) was found to exist in minor proportion (K_T=8.2, ΔG_{298}= −5.2 kJ mol^{-1}), whereas the 4*H*-form **12″** was not detected.

Benzotriazole has been shown to be a very effective auxiliary[8] and we attempted to apply 1-guanylbenzotriazole hydrochloride[9] as a guanylating agent[10] in the reaction with **12**. It was found that the guanylbenzotriazole selectively attacked endocyclic nitrogen N-1 of the triazole **12** affording **6** as hydrochloride, which was converted to the base using sodium carbonate. The target 7-amino-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**3**) were prepared in good yields via (5+1) heterocyclization of **6** using aldehydes or ketones **7** as one-carbon inserting reagents (Scheme 5, Table 2).

Both 5-amino-6,7-dihydro- and 7-amino-5,6-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazines (**2** and **3**) might be involved in the annular tautomerism (Scheme 6). However, the indicated forms were found to be predominant. The coupling of proton at sp^3-hybridized carbon and NH proton in ^1H NMR spectra was observed for several compounds (J=0–1.5 Hz). Despite

Table 2. 7-Amino-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**3**)

3	R^1	R^2	Yield (%)
a	H	Ph	78
b	H	4-MeO–C_6H_4	87
c	H	4-Me–C_6H_4	72
d	H	4-Cl–C_6H_4	70
e	H	4-F–C_6H_4	78
f	H	2-Furyl	70
g	H	4-Py	68
h	Me	Me	65
i		–$(CH_2)_4$–	62
j		–$(CH_2)_5$–	73

J value was small and not always detectable, 2D NOESY experiments clearly indicated that NH proton located in the vicinity of sp^3-hybridized carbon. The same tautomeric preferences were found in solid state as confirmed by X-ray crystallography of **2h** and **3h** (Figs. 2 and 3).[1,6] Interestingly, two almost identical individual molecules with the intermediate between a twist boat and a half-boat conformation were identified for compound **3h** in the crystal (Fig. 3).

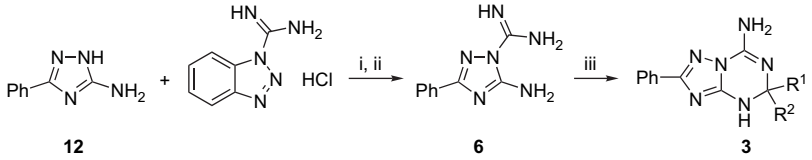
3. Conclusion

In summary, the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines with potential antifolate activity was successfully developed and their structures were investigated. The preparation method is practical: it required simple and easily available starting materials and provided derivatives of the interesting 5-azapurine system in 3–4 steps starting from benzhydrazide.

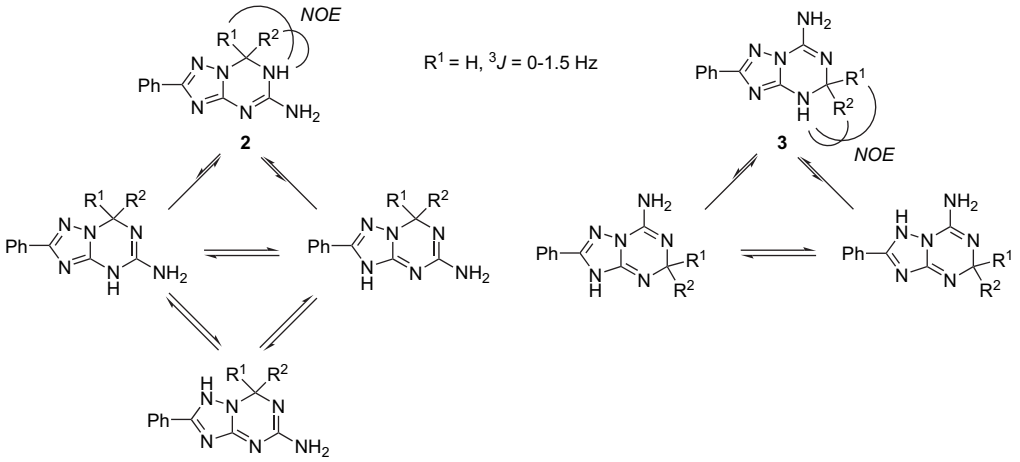
4. Experimental section

4.1. General

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. Analytical TLC were carried out on aluminum plates coated with Silica gel 60 F_{254}



Scheme 5. Reagents and conditions: (i) guanylbenzotriazole hydrochloride (1 equiv), EtOH, 30 min, reflux 62%; (ii) 10% Na_2CO_3, 25 °C (92%); (iii) **7a–g** (1 equiv) or **7i,j** (2 equiv), EtOH, piperidine (0.4 equiv), 2–15 h, reflux (62–87%); for **3h** acetone, piperidine (0.4 equiv), 12 h, reflux (65%).



Scheme 6. Tautomerism in 5(7)-amino-6,7(4,5)-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazines.

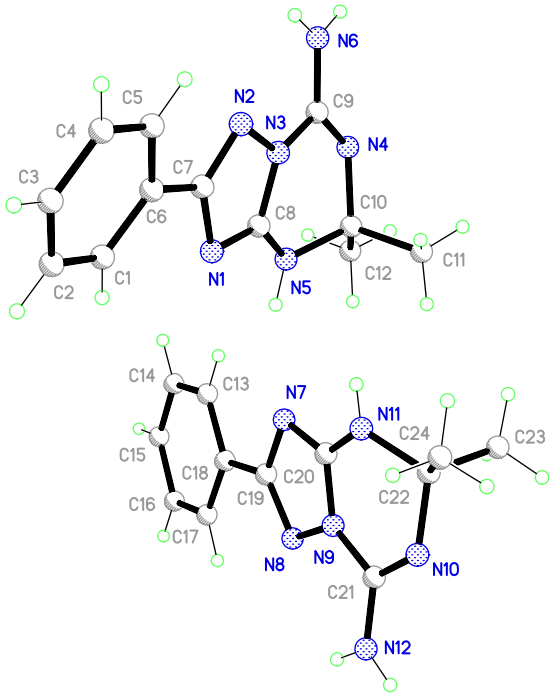


Figure 3. X-ray crystal structure of **3h**.

(Merck) with detection by UV light. Mass spectra were obtained on a Finnigan MAT LCQ LC–MS mass spectrometer using atmospheric pressure chemical ionization (APCI) mode. IR spectra were recorded in KBr pellets using a Shimadzu IRPrestige-21 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer using DMSO-d_6 as a solvent and TMS as an internal reference. The energy of activation ($\Delta G^{\ddagger}$) for the equilibrium between **11** and **11′** was estimated at the temperature of coalescence using dynamic ^{1}H NMR experiments (0.1 M solution in DMSO-d_6). The tautomeric preferences for **12** were investigated using ^{1}H NMR spectral data (0.1 M solution in DMSO-d_6 at 27 °C).

4.2. *N*-Benzamidobiguanide hydrochloride (8)[11]

To the solution of benzhydrazide (**1**, 6.80 g, 50 mmol) in EtOH (35 ml), concd HCl (5 ml, 50 mmol) and cyanoguanidine (4.62 g, 55 mmol) were added. The reaction mixture was heated under reflux with stirring for 4 h. After cooling on ice, the product was filtered, washed with cold EtOH, and dried to give white powder. White crystalline powder; yield 80%; mp 172–173 °C (EtOH) [lit.[11] mp 169–170 °C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.10 (br s, 4H, NH–C(=NH)NH$_2$), 7.51 (t, 2H, ^3J=7.3 Hz, H-3 and H-5), 7.60 (t, 1H, ^3J=7.2 Hz, H-4), 7.67 (br s, 2H, NH$_2$), 7.97 (d, 2H, ^3J=7.2 Hz, H-2 and H-6), 9.37 (br s, 1H, NH), 10.74 (br s, 1H, CONH).

4.3. *N*-(3-Phenyl-1*H*-1,2,4-triazol-5-yl)guanidine (9)[12]

N-Benzamidobiguanide hydrochloride (**8**, 5.13 g, 20 mmol) was heated at 80 °C in 10% aqueous sodium hydroxide solution (10 ml) for 6 h. After cooling, the product was filtered, washed with cold water, and dried. White crystalline powder; yield 68%; mp 242–243 °C [lit.[12] mp 244–246 °C]. TLC (silica gel, EtOH): R_f 0.16. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.58 (br s, 4H, NH–C(=NH)NH$_2$), 7.33 (t, 1H, ^3J=7.1 Hz, H-4′), 7.41 (t, 2H, ^3J=7.1 Hz, H-3′ and H-5′), 7.96 (d, 2H, ^3J=7.1 Hz, H-2′ and H-6′), 12.40 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.2 (2C), 128.0, 128.3 (2C), 139.2, 157.0, 157.7, 160.5.

4.4. *N*-Benzamidoguanidine (11)[7]

The mixture of benzhydrazide (**1**, 13.6 g, 100 mmol) and *S*-methylisothiouronium sulfate (13.9 g, 50 mmol) in 1% aqueous sodium hydroxide solution (400 ml) was stirred at rt for 72 h and then heated to 50 °C for another 3 h. After cooling, the precipitated product was filtered, washed with ice-cold water, and dried. White powder; yield 86%; mp 176 °C [lit.[7] mp 184 °C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (br s, 2H, NH$_2$), 7.16 (br s, 2H, NH$_2$), 7.23–7.35 (m, 3H, H-3, H-4 and H-5), 7.89–8.01 (m, 2H, H-2 and H-6), 11.01 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 126.5 (2C), 127.3 (2C), 128.0, 138.5, 152.9, 160.5.

4.5. 3(5)-Phenyl-1,2,4-triazol-5(3)-amine (12)[13]

N-Benzamidoguanidine (**11**, 8.90 g, 50 mmol) was heated under reflux in 80 ml of water for 4 h. After cooling, the precipitated amino-1,2,4-triazole **12** was filtered, washed with

ice-cold water, and dried. Colorless crystals; yield 97%; mp 186–187 °C [lit.[13] mp 186–187 °C]. TLC (silica gel, EtOH): R_f 0.59. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.29* and 6.05 (two br s, 2H, NH_2), 7.32 (t, 1H, ^3J=7.2 Hz, H-4′), 7.39 (t, 2H, ^3J=7.2 Hz, H-3′ and H-5′), 7.89 (d, 2H, ^3J=6.8 Hz, H-2′ and H-6′), 12.04 and 13.20* (two br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.2 (2C), 128.0, 128.2 (2C), 132.3, 157.2, 158.3. *, Signals of the minor tautomeric form.

4.6. 1-Guanylbenzotriazole hydrochloride[14]

To the stirred mixture of benzotriazole (8.9 g, 75 mmol) and cyanamide (6.3 g, 150 mmol) at 100 °C, concd HCl (8.5 ml, 85 mmol) was added. After initial vigorous reaction, the mixture was heated for 15 min at 100 °C. Then, 1 M HCl (12 ml) was added. After cooling, the precipitated 1-guanylbenzotriazole hydrochloride was filtered, washed with ice-cold 1 M HCl, and dried. White powder; yield 68%; mp 194–196 °C [lit.[14] mp 195–197 °C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.67 (t, 1H, ^3J=7.7 Hz, H-3), 7.87 (t, 1H, ^3J=7.7 Hz, H-5), 8.08 (d, 1H, ^3J=8.3 Hz, H-4), 8.32 (d, 1H, ^3J=8.3 Hz, H-7), 10.23 (s, 4H, C(=NH)NH_2·HCl). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.8, 120.2, 126.5, 130.4, 130.5, 145.6, 152.1.

4.7. 1-Guanyl-3-phenyl-1,2,4-triazol-5-amine hydrochloride (6·HCl)[9b]

To the solution of 3(5)-phenyl-1,2,4-triazol-5(3)-amine (**12**, 6.80 g, 40 mmol) in EtOH (35 ml), 1-guanylbenzotriazole hydrochloride (7.88 g, 40 mmol) was added. The reaction mixture was heated under reflux with stirring for 30 min. After cooling, the product was filtered, washed with cold EtOH, and dried. White crystalline powder; yield 62%; mp 212 °C [lit.[9b] mp 210 °C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.46–7.56 (m, 3H, H-3′, H-4′ and H-5′), 7.71 (s, 2H, NH_2), 8.00 (dd, 2H, ^3J=6.4, ^4J=3.0 Hz, H-2′ and H-6′), 9.47 (s, 4H, C(=NH)NH_2·HCl). ^{13}C NMR (75 MHz, DMSO-d_6): δ 126.4 (2C), 128.7 (2C), 129.4, 130.3, 151.9, 157.0, 160.8.

4.8. 1-Guanyl-3-phenyl-1,2,4-triazol-5-amine (6)[9b]

The sodium carbonate solution (10%, 30 ml) was added to the solution of 1-guanyl-3-phenyl-1,2,4-triazol-5-amine hydrochloride (**6·HCl**, 5.95 g, 25 mmol) in water (15 ml). After cooling, the product was filtered, washed with cold water, and dried. White powder; yield 92%; mp 168 °C [lit.[9b] mp 165 °C]. TLC (silica gel, EtOH): R_f 0.59. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.36 (s, 1H, NH), 6.54 (s, 2H, NH_2), 7.37–7.53 (m, 3H, H-3′, H-4′ and H-5′), 7.88 (s, 2H, NH_2), 7.98 (dd, 2H, ^3J=7.3, ^4J=1.7 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.9 (2C), 128.4 (2C), 129.2, 130.7, 152.7, 156.6, 156.8.

4.9. General method for preparation of 7-(het)aryl-2-phenyl-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-amines (2a–g)

The solution of *N*-(3-phenyl-1*H*-1,2,4-triazol-5-yl)guanidine (**5**, 0.50 g, 2.5 mmol), appropriate aldehyde (**7a–g**, 2.5 mmol), and piperidine (0.10 ml, 1.0 mmol) in EtOH (7–10 ml) was heated under reflux for 3–18 h. After cooling, the product was filtered, washed with cold EtOH, dried, and recrystallized from EtOH, DMF or their mixture.

4.9.1. 2,7-Diphenyl-6,7-dihydro[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazin-5-amine (2a). White crystalline powder; yield 92%; mp 300–301 °C. TLC (silica gel, EtOH): R_f 0.57. LC–MS (APCI) *m*/*z* 291 (MH^+). Anal. Calcd for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.02; H, 4.95; N, 28.73%. IR (KBr): ν 3461, 3311, 3237, 3135, 1653, 1646, 1597, 1548, 1522 (m), 1474, 1460, 1444, 1434, 1411, 1371, 764, 747, 713, 691 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.42 (s, 2H, NH_2), 6.69 (s, 1H, H-7), 7.29–7.47 (m, 8H, H-3′, H-4′, H-5′ and 5-Ph), 7.86 (dd, 2H, ^3J=7.9, ^4J=1.5 Hz, H-2′ and H-6′), 7.93 (d, 1H, ^3J=1.5 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 68.3, 125.3 (2C), 126.2 (2C), 128.3 (2C), 128.4, 128.7 (2C), 129.0, 131.7, 140.4, 155.5, 156.4, 159.2.

4.9.2. 7-(4-Methoxylphenyl)-2-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-amine (2b). White crystalline powder; yield 91%; mp 291 °C. TLC (silica gel, EtOH): R_f 0.54. LC–MS (APCI) *m*/*z* 321 (MH^+). Anal. Calcd for $C_{17}H_{16}N_6O$: C, 63.74; H, 5.03; N, 4.99. Found: C, 63.70; H, 5.12; N, 4.91%. IR (KBr): ν 3451, 3309, 3227, 3110, 1653, 1647, 1594, 1523 (m), 1477, 1435, 1409, 1369, 1254, 1178, 815, 746, 688 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H, OMe), 6.39 (s, 2H, NH_2), 6.63 (d, 1H, ^3J=0.8 Hz, H-7), 6.97 (d, 2H, ^3J=8.7 Hz, H-3″ and H-5″), 7.28 (d, 2H, ^3J=8.7 Hz, H-2″ and H-6″), 7.35 (t, 2H, ^3J=7.5 Hz, H-3′ and H-5′), 7.37 (t, 1H, ^3J=7.5 Hz, H-4′), 7.86 (d, 2H, ^3J=7.5 Hz, H-2′ and H-6′), 7.87 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1, 68.0, 114.0 (2C), 125.3 (2C), 127.6 (2C), 128.3 (2C), 128.4, 131.8, 132.5, 155.5, 156.3, 159.1, 159.7.

4.9.3. 7-(4-Methylphenyl)-2-phenyl-6,7-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-5-amine (2c). White crystalline powder; yield 90%; mp 281 °C. TLC (silica gel, EtOH): R_f 0.57. LC–MS (APCI) *m*/*z* 305 (MH^+). Anal. Calcd for $C_{17}H_{16}N_6$: C, 67.09; H, 5.30; N, 27.61. Found: C, 66.92; H, 5.34; N, 27.55%. IR (KBr): ν 3462, 3311, 3231, 3111, 1652, 1648, 1599, 1522 (m), 1477, 1444, 1435, 1409, 1365, 805, 745, 689 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, Me), 6.40 (s, 2H, NH_2), 6.65 (d, 1H, ^3J= 1.5 Hz, H-7), 7.20–7.25 (m, 4H, H-2″, H-3″, H-5″ and H-6″), 7.32–7.41 (m, 3H, H-3′, H-4′ and H-5′), 7.86 (dd, 2H, ^3J=8.1, ^4J=1.7 Hz, H-2′ and H-6′), 7.89 (d, 1H, ^3J= 1.5 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.7, 68.2, 125.3 (2C), 126.2 (2C), 128.3 (2C), 128.4, 129.2 (2C), 131.8, 137.6, 138.5, 155.5, 156.3, 159.1.

4.9.4. 7-(4-Chlorophenyl)-2-phenyl-6,7-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-5-amine (2d). White crystalline powder; yield 73%; mp 290 °C. TLC (silica gel, EtOH): R_f 0.56. LC–MS (APCI) *m*/*z* 325, 327 (MH^+). Anal. Calcd for $C_{16}H_{13}ClN_6$: C, 59.17; H, 4.03; N, 25.88. Found: C, 59.02; H, 4.19; N, 25.73%. IR (KBr): ν 3446, 3309, 3237, 3111, 1653, 1647, 1595, 1525 (m), 1472, 1433, 1396, 1363, 745, 689 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.48 (s, 2H, NH_2), 6.74 (s, 1H, H-7), 7.29–7.44 (m, 5H, H-2″, H-6″, H-3′, H-4′ and H-5′), 7.51 (d, 2H, ^3J=8.3 Hz, H-3″ and H-5″), 7.87 (d, 2H, ^3J=7.5 Hz,

H-2′ and H-6′), 7.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.6, 125.4 (2C), 128.2 (2C), 128.3 (2C), 128.5, 128.8 (2C), 131.7, 133.6, 139.3, 155.4, 156.4, 159.4.

4.9.5. 7-(4-Fluorophenyl)-2-phenyl-6,7-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-5-amine (2e). White crystalline powder; yield 76%; mp 280–281 °C. TLC (silica gel, EtOH): R_f 0.56. LC–MS (APCI) *m*/*z* 309 (MH^+). Anal. Calcd for $C_{16}H_{13}FN_6$: C, 62.33; H, 4.25; N, 27.26. Found: C, 62.21; H, 4.34; N, 27.19%. IR (KBr): ν 3469, 3310, 3236, 3112, 1653, 1647, 1601, 1524 (m), 1476, 1436, 1409, 1363, 1239, 821, 746, 688 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.45 (s, 2H, NH_2), 6.73 (s, 1H, H-7), 7.27 (dd, 2H, $^3J_{HF}$=8.9, ^3J=8.9 Hz, H-3″ and H-5″), 7.32–7.47 (m, 5H, H-3′, H-4′, H-5′, H-2″ and H-6″), 7.86 (d, 2H, ^3J=7.5 Hz, H-2′ and H-6′), 7.94 (d, 1H, ^3J=1.5 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.6, 115.6 (d, $^2J_{CF}$=21.8 Hz, 2C), 125.4 (2C), 128.3 (2C), 128.5, 127.5 (d, $^3J_{CF}$=8.8 Hz, 2C), 131.7, 136.7 (d, $^4J_{CF}$=2.9 Hz), 155.5, 156.4, 159.4, 162.3 (d, $^1J_{CF}$=245.2 Hz).

4.9.6. 7-(2-Furyl)-2-phenyl-6,7-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-5-amine (2f). Beige crystalline powder; yield 72%; mp 272 °C. TLC (silica gel, EtOH): R_f 0.56. LC–MS (APCI) *m*/*z* 281 (MH^+). Anal. Calcd for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.98. Found: C, 59.78; H, 4.43; N, 29.89%. IR (KBr): ν 3472, 3448, 3313, 3232, 3105, 1655, 1651, 1603, 1523 (m), 1477, 1436, 1395, 1364, 830, 750, 693 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.45 (s, 2H, NH_2), 6.47 (dd, 1H, ^3J=3.1, ^3J=1.7 Hz, H-4″), 6.54 (d, 1H, ^3J=3.1 Hz, H-3″), 6.81 (s, 1H, H-7), 7.30–7.45 (m, 3H, H-3′, H-4′ and H-5′), 7.68 (d, 1H, ^3J=1.7 Hz, H-5″), 7.88 (dd, 2H, ^3J=7.5, ^4J=1.5 Hz, H-2′ and H-6′), 7.92 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 62.2, 108.7, 110.5, 125.4 (2C), 128.3 (2C), 128.5, 131.7, 143.8, 151.5, 155.5, 156.3, 159.3.

4.9.7. 2-Phenyl-7-(4-pyridyl)-6,7-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-5-amine (2g). Yellowish crystalline powder; yield 78%; mp 242–244 °C. TLC (silica gel, EtOH): R_f 0.30. LC–MS (APCI) *m*/*z* 292 (MH^+). Anal. Calcd for $C_{15}H_{13}N_7$: C, 61.84; H, 4.50; N, 33.66. Found: C, 61.63; H, 4.62; N, 33.50%. IR (KBr): ν 3447, 3324, 3107, 3079, 1653, 1647, 1624, 1606, 1521 (m), 1437, 1420, 1362, 1295, 741, 685 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.56 (s, 2H, NH_2), 6.77 (s, 1H, H-7), 7.23–7.48 (m, 5H, H-2″, H-6″, H-3′, H-4′ and H-5′), 7.89 (d, 2H, ^3J=7.5 Hz, H-2′ and H-6′), 8.06 (s, 1H, NH), 8.64 (d, 2H, ^3J=5.3 Hz, H-3″ and H-5″). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.0, 120.9 (2C), 125.4 (2C), 128.3 (2C), 128.6, 131.6, 148.2, 150.2 (2C), 155.5, 156.4, 159.6.

4.9.8. 7,7-Dimethyl-2-phenyl-6,7-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-5-amine (2h). The mixture of *N*-(3-phenyl-1*H*-1,2,4-triazol-5-yl)guanidine (**5**, 0.50 g, 2.5 mmol) and piperidine (0.10 ml, 1.0 mmol) in acetone (7 ml) was heated under reflux for 18 h. After cooling, the precipitated product was filtered, washed with acetone, dried, and recrystallized from EtOH. White crystalline powder; yield 98%; mp 294 °C. TLC (silica gel, EtOH): R_f 0.50. LC–MS (APCI) *m*/*z* 243 (MH^+). Anal. Calcd for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.45; H, 5.86; N, 34.64%. IR (KBr): ν 3473, 3308, 3230, 3055, 2977, 1654, 1651, 1616, 1559, 1528 (m), 1476, 1460, 1444, 1420, 1362, 1172, 748, 699, 691, 476 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (s, 6H, Me_2), 6.21 (s, 2H, NH_2), 7.36–7.40 (m, 3H, H-3′, H-4′ and H-5′), 7.58 (s, 1H, NH), 7.92 (dd, 2H, ^3J=8.3, ^4J=1.5 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.7 (2C), 70.1, 125.3 (2C), 128.3 (3C), 132.1, 155.5, 155.8, 158.7.

4.10. General method for preparation of the spiro derivatives of 2-phenyl-6,7-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-5-amines (2i,j)

The solution of *N*-(3-phenyl-1*H*-1,2,4-triazol-5-yl)guanidine (**9**, 0.50 g, 2.5 mmol), appropriate cyclic ketone (**7i,j**, 5.0 mmol), and piperidine (0.10 ml, 1.0 mmol) in EtOH (8 ml) was heated under reflux for 16–24 h. After cooling, the product was filtered, washed with cold EtOH, dried, and recrystallized from EtOH/DMF.

4.10.1. 2′-Phenyl-6′*H*-spiro[cyclopentane-1,7′-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin]-5′-amine (2i). White crystalline powder; yield 96%; mp 300 °C. TLC (silica gel, EtOH): R_f 0.54. LC–MS (APCI) *m*/*z* 269 (MH^+). Anal. Calcd for $C_{14}H_{16}N_6$: C, 62.67; H, 6.01; N, 31.32. Found: C, 62.46; H, 6.17; N, 31.19%. IR (KBr): ν 3471, 3280, 3204, 3123, 2962, 1653, 1635, 1630, 1598, 1523 (m), 1473, 1435, 1419, 1362, 753, 703 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.71–1.97 (m, 6H, $(CH_2)_2$, H-2*a* and H-5*a*), 2.21–2.37 (m, 2H, H-2*e* and H-5*e*), 6.20 (s, 2H, NH_2), 7.34 (t, 1H, ^3J=7.0 Hz, H-4′), 7.46 (t, 2H, ^3J=7.2 Hz, H-3′ and H-5′), 7.73 (s, 1H, NH), 7.92 (d, 2H, ^3J=7.2 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.0 (2C), 39.6 (2C), 79.6, 125.3 (2C), 128.3 (3C), 132.0, 155.5, 156.2, 158.7.

4.10.2. 2′-Phenyl-6′*H*-spiro[cyclohexane-1,7′-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin]-5′-amine (2j). White crystalline powder; yield 72%; mp 283 °C. TLC (silica gel, EtOH): R_f 0.58. LC–MS (APCI) *m*/*z* 283 (MH^+). Anal. Calcd for $C_{15}H_{18}N_6$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.72; H, 6.65; N, 29.58%. IR (KBr): ν 3463, 3363, 3309, 3134, 2933, 1653, 1647, 1636, 1587, 1558, 1534, 1521 (m), 1473, 1444, 1409, 1356, 753, 710, 693 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22–1.71 (m, 8H, $(CH_2)_3$, H-2*a* and H-6*a*), 2.00–2.18 (m, 2H, H-2*e* and H-6*e*), 6.28 (s, 2H, NH_2), 7.30–7.45 (m, 3H, H-3′, H-4′ and H-5′), 7.45 (s, 1H, NH), 7.92 (dd, 2H, ^3J=8.0, ^4J=1.5 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.8 (2C), 24.0, 36.4 (2C), 71.2, 125.3 (2C), 128.3 (3C), 132.1, 155.5, 155.8, 158.5.

4.11. General method for preparation of 5-(het)aryl-2-phenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amines (3a–g)

The solution of 1-guanyl-3-phenyl-1,2,4-triazol-5-amine (**6**, 0.50 g, 2.5 mmol), appropriate aldehyde (**7a–g**, 2.5 mmol), and piperidine (0.10 ml, 1.0 mmol) in EtOH (7–10 ml) was heated under reflux for 2–12 h. After cooling, the product was filtered, washed with cold EtOH, dried, and recrystallized from EtOH, DMF or their mixture.

4.11.1. 2,5-Diphenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazin-7-amine (3a). White crystalline powder;

yield 78%; mp 204–205 °C. TLC (silica gel, EtOH): R_f 0.62. LC–MS (APCI) *m/z* 291 (MH^+). Anal. Calcd for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.05; H, 5.07; N, 28.73%. IR (KBr): ν 3437, 3231, 3133, 1706, 1697, 1626, 1531, 1495, 1450, 1434, 1340, 1026, 730, 701, 685 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 5.91 (s, 1H, H-5), 6.60 (s, 2H, NH_2), 7.25–7.53 (m, 8H, H-3′, H-4′, H-5′ and 5-Ph), 8.00 (dd, 2H, ^3J=7.3, ^4J=2.4 Hz, H-2′ and H-6′), 8.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 68.2, 126.2 (2C), 126.3 (2C), 127.7, 128.1 (2C), 128.5 (2C), 129.6, 130.5, 142.9, 143.4, 156.1, 159.8.

4.11.2. 5-(4-Methoxyphenyl)-2-phenyl-4,5-dihydro-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine (3b). White crystalline powder; yield 87%; mp 212 °C. TLC (silica gel, EtOH): R_f 0.55. LC–MS (APCI) *m/z* 321 (MH^+). Anal. Calcd for $C_{17}H_{16}N_6O$: C, 63.74; H, 5.03; N, 4.99. Found: C, 63.60; H, 5.23; N, 4.81%. IR (KBr): ν 3439, 3231, 3126, 1706, 1697, 1624, 1534, 1511, 1499, 1451, 1437, 1343, 1252, 1036, 737, 690 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H, OMe), 5.84 (s, 1H, H-5), 6.54 (s, 2H, NH_2), 6.92 (d, 2H, ^3J=8.7 Hz, H-3″ and H-5″), 7.37 (d, 2H, ^3J=8.7 Hz, H-2″ and H-6″), 7.42–7.52 (m, 3H, H-3′, H-4′ and H-5′), 7.98 (dd, 2H, ^3J=7.2, ^4J= 2.3 Hz, H-2′ and H-6′), 8.58 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0, 67.8, 113.4 (2C), 126.2 (2C), 127.5 (2C), 128.5 (2C), 129.6, 130.5, 135.0, 143.4, 156.1, 158.7, 159.8.

4.11.3. 5-(4-Methylphenyl)-2-phenyl-4,5-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-7-amine (3c). White crystalline powder; yield 72%; mp 213–214 °C. TLC (silica gel, EtOH): R_f 0.58. LC–MS (APCI) *m/z* 305 (MH^+). Anal. Calcd for $C_{17}H_{16}N_6$: C, 67.09; H, 5.30; N, 27.61. Found: C, 66.86; H, 5.52; N, 27.53%. IR (KBr): ν 3440, 3224, 3125, 1702, 1696, 1624, 1532, 1496, 1452, 1437, 1343, 1034, 758, 735, 686 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, Me), 5.86 (s, 1H, H-5), 6.56 (s, 2H, NH_2), 7.17 (d, 2H, ^3J=7.9 Hz, H-3″ and H-5″), 7.32 (d, 2H, ^3J=7.9 Hz, H-2″ and H-4″), 7.41–7.51 (m, 3H, H-3′, H-4′ and H-5′), 7.98 (dd, 2H, ^3J=7.2, ^4J=2.2 Hz, H-2′ and H-6′), 8.61 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6, 68.0, 126.1 (2C), 126.2 (2C), 128.5 (2C), 128.6 (2C), 129.6, 130.5, 136.8, 140.0, 143.4, 156.1, 159.8.

4.11.4. 5-(4-Chlorophenyl)-2-phenyl-4,5-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-7-amine (3d). White crystalline powder; yield 70%; mp 220–221 °C. TLC (silica gel, EtOH): R_f 0.60. LC–MS (APCI) *m/z* 325, 327 (MH^+). Anal. Calcd for $C_{16}H_{13}ClN_6$: C, 59.17; H, 4.03; N, 25.88. Found: C, 58.94; H, 4.32; N, 25.62%. IR (KBr): ν 3444, 3228, 3124, 1705, 1697, 1628, 1533, 1498, 1490, 1454, 1437, 1343, 1018, 773, 737, 689 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 5.92 (s, 1H, H-5), 6.62 (s, 2H, NH_2), 7.39–7.54 (m, 7H, H-3′, H-4′, H-5′, H-2″, H-3″, H-5″ and H-6″), 7.99 (dd, 2H, ^3J=7.2, ^4J=1.9 Hz, H-2′ and H-6′), 8.67 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.6, 126.2 (2C), 128.1 (2C), 128.2 (2C), 128.5 (2C), 129.6, 130.4, 132.2, 141.9, 143.6, 156.0, 159.9.

4.11.5. 5-(4-Fluorophenyl)-2-phenyl-4,5-dihydro[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-7-amine (3e). White crystalline powder; yield 78%; mp>360 °C. TLC (silica gel, EtOH): R_f 0.63. LC–MS (APCI) *m/z* 309 (MH^+). Anal. Calcd for $C_{16}H_{13}FN_6$: C, 62.33; H, 4.25; N, 27.26. Found: C, 62.02; H, 4.47; N, 27.11%. IR (KBr): ν 3441, 3225, 3134, 1706, 1697, 1627, 1601, 1532, 1507, 1496, 1449, 1436, 1340, 1227, 1034, 771, 736, 687 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 5.93 (s, 1H, H-5), 6.63 (s, 2H, NH_2), 7.20 (dd, 2H, $^3J_{HF}$=8.9, ^3J=8.9 Hz, H-3″ and H-5″) 7.43–7.54 (m, 5H, H-3′, H-4′, H-5′, H-2″ and H-6″), 8.00 (dd, 2H, ^3J=7.3, ^4J=2.4 Hz, H-2′ and H-6′), 8.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.6, 114.9 (d, $^2J_{CF}$=21.8 Hz, 2C), 126.2 (2C), 128.4 (d, $^3J_{CF}$=8.2 Hz, 2C), 128.5 (2C), 129.6, 130.5, 139.1 (d, $^4J_{CF}$=2.9 Hz), 143.6, 156.1, 159.9, 161.6 (d, $^1J_{CF}$=243.4 Hz).

4.11.6. 5-Furyl-2-phenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazin-7-amine (3f). Beige crystalline powder; yield 70%; mp 210 °C. TLC (silica gel, EtOH): R_f 0.62. LC–MS (APCI) *m/z* 281 (MH^+). Anal. Calcd for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.98. Found: C, 59.83; H, 4.46; N, 29.84%. IR (KBr): ν 3305, 3240, 3159, 1702, 1698, 1637, 1529, 1457, 1438, 1342, 1233, 1015, 755 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 5.94 (d, 1H, ^3J=1.1 Hz, H-5), 6.29 (d, 1H, ^3J=3.0 Hz, H-5″), 6.40 (dd, 1H, ^3J=3.0, ^3J=1.8 Hz, H-4″), 6.63 (s, 2H, NH_2), 7.41–7.52 (m, 3H, H-′, H-4′ and H-5′), 7.59 (d, 1H, ^3J=1.8 Hz, H-3″), 7.99 (dd, 2H, ^3J=7.3, ^4J=2.4 Hz, H-2′ and H-6′), 8.74 (d, 1H, ^3J=1.1 Hz, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 62.3, 105.8, 110.1, 126.1 (2C), 128.5 (2C), 129.6, 130.4, 142.4, 144.2, 154.9, 155.5, 159.6.

4.11.7. 2-Phenyl-5-(4-pyridyl)-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine (3g). Yellowish crystalline powder; yield 68%; mp 333–335 °C. TLC (silica gel, EtOH): R_f 0.38. LC–MS (APCI) *m/z* 292 (MH^+). Anal. Calcd for $C_{15}H_{13}N_7$: C, 61.84; H, 4.50; N, 33.66. Found: C, 61.63; H, 4.76; N, 33.52%. IR (KBr): ν 3442, 3230, 3126, 1705, 1697, 1625, 1533, 1496, 1453, 1436, 1416, 1340, 1036, 771, 735, 685 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 5.96 (s, 1H, H-5), 6.72 (s, 2H, NH_2), 7.39–7.54 (m, 5H, H-3′, H-4′, H-5′, H-2″ and H-6″), 8.00 (dd, 2H, ^3J=7.0, ^4J= 2.4 Hz, H-2′ and H-6′), 8.59 (dd, 2H, ^3J=4.7, ^4J=1.3 Hz, H-3″ and H-5″), 8.81 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.1, 121.3 (2C), 126.2 (2C), 128.5 (2C), 129.7, 130.4, 143.8, 149.7 (2C), 151.1, 155.9, 159.9.

4.11.8. 5,5-Dimethyl-2-phenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-amine (3h). The mixture of 1-guanyl-3-phenyl-1,2,4-triazol-5-amine (**6**, 0.50 g, 2.5 mmol) and piperidine (0.10 ml, 1.0 mmol) in acetone (7 ml) was heated under reflux for 12 h. After cooling, the precipitated product was filtered, washed with acetone, dried, and recrystallized from EtOH. White crystalline powder; yield 65%; mp 210 °C. TLC (silica gel, EtOH): R_f 0.55. LC–MS (APCI) *m/z* 243 (MH^+). Anal. Calcd for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.31; H, 6.03; N, 34.56%. IR (KBr): ν 3414, 3388, 3072, 2965, 1705, 1698, 1624, 1522, 1495, 1448, 1431, 1380 (d, *gem*-Me_2), 1340, 913, 740, 705, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.37 (s, 6H, Me_2), 6.30 (s, 2H, NH_2), 7.42–7.51 (m, 3H, H-3′, H-4′ and H-5′), 7.98 (dd, 2H, ^3J=7.2, ^4J=1.9 Hz, H-2′ and H-6′), 8.25 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.5 (2C), 68.8, 126.1 (2C), 128.5 (2C), 129.5, 130.7, 141.5, 155.4, 159.5.

4.12. General method for preparation of the spiro derivatives of 2-phenyl-4,5-dihydro[1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-7-amines (3i,j)

The solution of 1-guanyl-3-phenyl-1,2,4-triazol-5-amine (**6**, 0.50 g, 2.5 mmol), appropriate cyclic ketone (**7i,j**, 5.0 mmol), and piperidine (0.10 ml, 1.0 mmol) in EtOH (8 ml) was heated under reflux for 10–15 h. After cooling, the product was filtered, washed with cold EtOH, dried, and recrystallized from EtOH.

4.12.1. 2′-Phenyl-4′*H*-spiro[cyclopentane-1,5′-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin]-7′-amine (3i). White crystalline powder; yield 62%; mp 206–207 °C. TLC (silica gel, EtOH): R_f 0.60. LC–MS (APCI) *m/z* 269 (MH^+). Anal. Calcd for $C_{14}H_{16}N_6$: C, 62.67; H, 6.01; N, 31.32. Found: C, 62.50; H, 6.22; N, 31.16%. IR (KBr): ν 3389, 3246, 3074, 2959, 1702, 1698, 1628, 1527, 1494, 1452, 1436, 1374, 1344, 743, 690 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.62–1.87 (m, 8H, $(CH_2)_4$), 6.30 (s, 2H, NH_2), 7.39–7.52 (m, 3H, H-3′, H-4′ and H-5′), 7.98 (dd, 2H, ^3J=7.5, ^4J= 1.9 Hz, H-2′ and H-6′), 8.33 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.2 (2C), 41.0 (2C), 78.9, 126.1 (2C), 128.5 (2C), 129.5, 130.7, 141.7, 155.9, 159.6.

4.12.2. 2′-Phenyl-4′*H*-spiro[cyclohexane-1,5′-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin]-7′-amine (3j). White crystalline powder; yield 73%; mp 216–217 °C. TLC (silica gel, EtOH): R_f 0.59. LC–MS (APCI) *m/z* 283 (MH^+). Anal. Calcd for $C_{15}H_{18}N_6$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.57; H, 6.53; N, 29.64%. IR (KBr): ν 3374, 3287, 3072, 2936, 2922, 1702, 1698, 1635, 1527, 1491, 1451, 1430, 1354, 746, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.25–1.81 (m, 10H, $(CH_2)_5$), 6.31 (s, 2H, NH_2), 7.39–7.54 (m, 3H, H-3′, H-4′ and H-5′), 7.99 (dd, 2H, ^3J=7.3, ^4J= 1.7 Hz, H-2′ and H-6′), 8.20 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3 (2C), 25.0, 38.9 (2C), 70.3, 126.1 (2C), 128.5 (2C), 129.5, 130.7, 141.2, 155.6, 159.6.

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