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SYNTHESIS OF 5,7-DIAMINO[1,2,4]TRIAZOLO[1,2-*a*][1,3,5]TRIAZINES VIA ANNULATION OF 1,3,5-TRIAZINE RING ONTO 3(5)-AMINO-1,2,4-TRIAZOLES[1]

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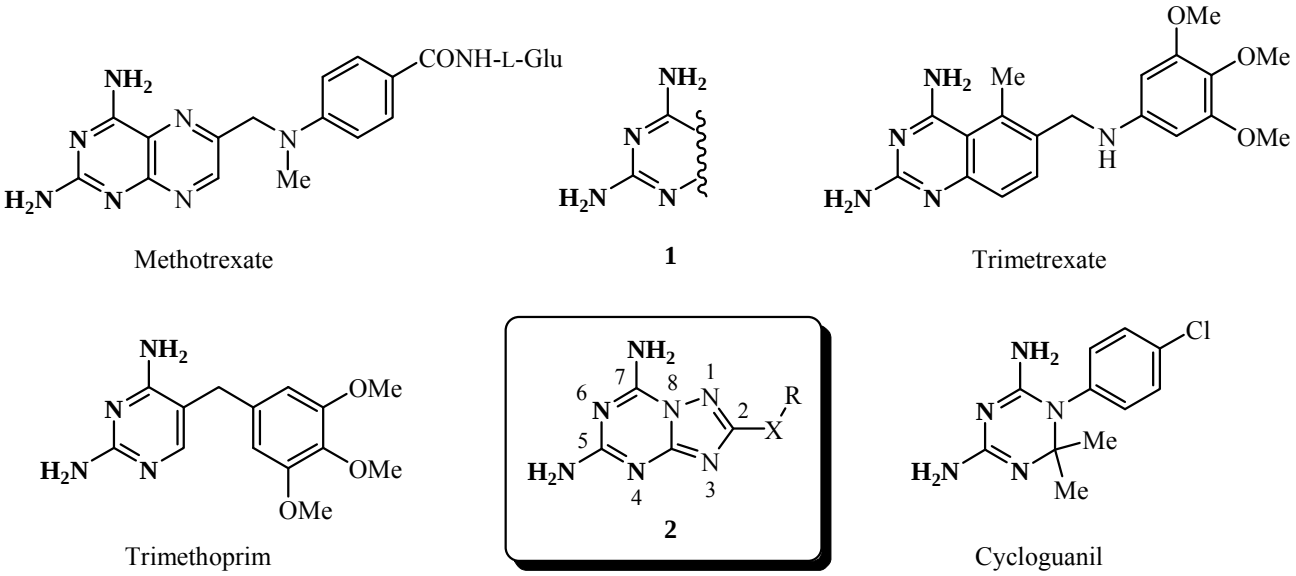
Abstract – The 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines were synthesized by cyclocondensation of 3(5)-amino-1,2,4-triazoles with cyanoguanidine. The substituted 3(5)-amino-1,2,4-triazoles were prepared from corresponding hydrazides and *S*-methylisothiourea via ring closure of the intermediate acylaminoguanidines. The 3,5-diamino-1,2,4-triazoles were prepared using partial aminolysis of dimethyl *N*-cyanodithiocarbonimidate followed by cyclization of the obtained *N*-substituted *N'*-cyano-*S*-methylisothioureas with hydrazine. The structures of the prepared compound were confirmed using NMR spectral data.

INTRODUCTION

Most of the known antifolate drugs such as methotrexate, trimethoprim, cycloguanil and trimetrexate possess the diamino heterocyclic fragment (**1**) in their molecular structures (Figure). The diamino heterocyclic structure (**1**) forms an essential part of the pharmacophore in the molecules of dihydrofolate reductase (DHFR) inhibitors that have found applications for chemotherapy of cancer or infectious diseases.[2] Our group has been working on the synthesis of fused 1,3,5-triazines as potential inhibitors of DHFR.[3,4] In continuation of these investigations we became interested in the synthesis of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine heterocyclic system, which is the 5-aza- analogue of the purine scaffold.[5] This report describes the synthesis of 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2**) which contain the pharmacophoric structure (**1**) (Figure). In addition, lipophilic aromatic moiety that is a common feature in the side chain as a distal part of the "nonclassical" DHFR inhibitors, is also included in the series of compounds synthesized. The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus is ether linked to the lipophilic aromatic part directly or has a spacer linker (X) introduced between the heterocyclic skeleton and lypophilic part (R).



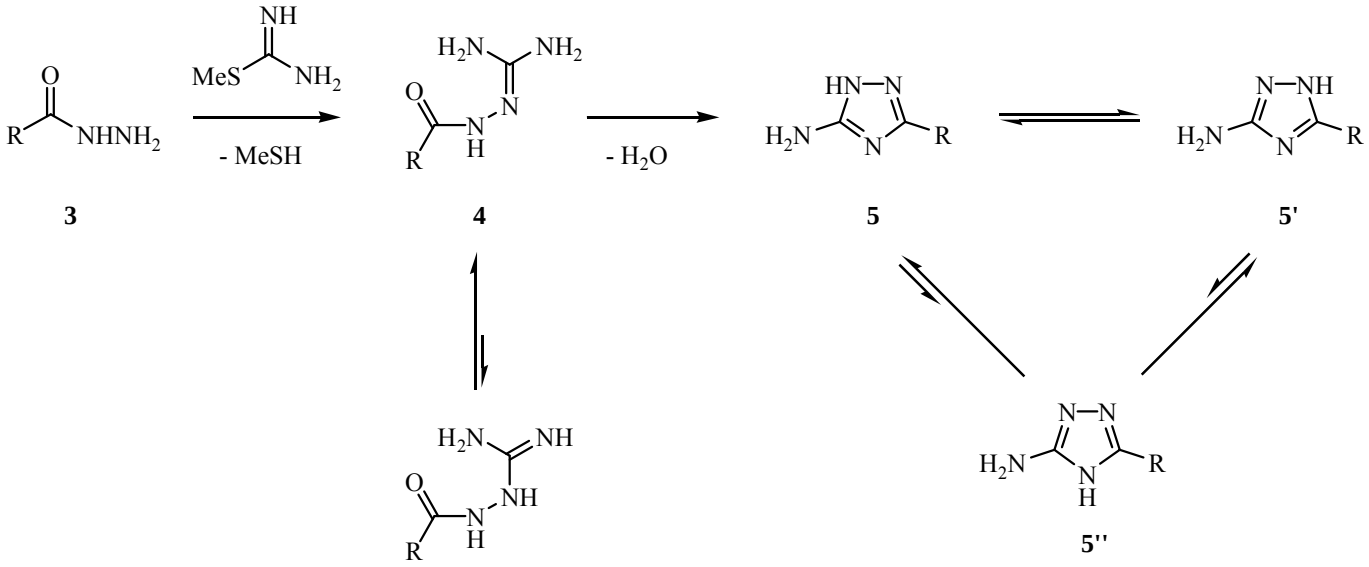
Figure

RESULTS AND DISCUSSION

It has been shown[5] that 3(5)-amino-1,2,4-triazoles may serve as building blocks for the preparation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazines. We used two general approaches for the synthesis of these key intermediates.

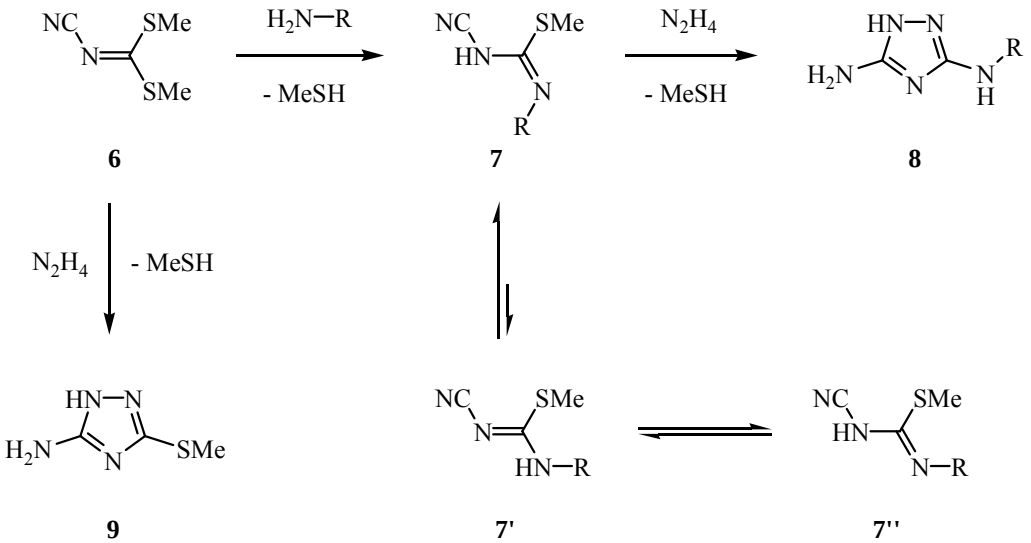
The reaction of hydrazides (**3**) with isothiourea in water provided acylaminoguanidines (**4a-c**) (Scheme 1). Phenylacetamidoguanidine (**4a**) was readily cyclyzed to benzyl substituted 1,2,4-triazole (**5a**) at the reaction conditions and therefore was not isolated. The (het)arylamidoguanidines (**4b,c**) were found to be stable: they can be recrystallized from water and did not change after drying under vacuum at 140ºC for 24 h. The two signals of NH_2 groups in ^{1}H NMR spectra of the compounds obtained **4b,c** indicated that tautomeric form **4**, rather than form **4'**, was preferred in DMSO solution.

When (het)arylamidoguanidines (**4b,c**) were heated in water, 3(5)-amino-1,2,4-triazoles (**5b,c**) were obtained in almost quantitative yields (Table 1). The reaction was found to be clean and afforded products (**5b,c**) with satisfactory purity. Annular tautomerism is possible in the prepared triazoles **(5a-c**); theoretically, they may exist in three tautomeric forms (**5**, **5'** and **5''**). A study of the triazoles (**5a-c**) in DMSO solution using ^{1}H NMR spectroscopy (Table 2) concluded that 5-amino-1,2,4-triazoles (**5**) predominated in the equilibrium, while 3-amino-1,2,4-triazoles (**5'**) was found to exist in minor proportion. No signals to support the presence of form **5''** were found in ^{1}H NMR spectra. The tautomeric equilibrium constant ($K_{T(5/5')}$) and the relative Gibbs free energies (ΔG_{298}) of individual tautomers **5** and **5'** were determined in DMSO solution using ^{1}H NMR spectroscopy. For benzyl substituted 1,2,4-triazole (**5a**) $K_{T(5/5')}$ was equal 4, ΔG_{298} was found to be -3.4 kJ mol^{-1}, for phenyl and 4-pyridyl substituted 1,2,4-triazoles (**5b,c**) these parameters were 9 (-5.4 kJ mol^{-1}) and 33 (-8.7 kJ mol^{-1}) respectively.



Scheme 1

The reaction of dimethyl *N*-cyanodithiocarbonimidate (**6**) with aryl- or arylalkylamines afforded the corresponding *N*-substituted *N'*-cyano-*S*-methylisothioureas (**7**) (Scheme 2). The splitting pattern of the methylene protons signals in ^{1}H NMR spectra of **7b,c** did not suggest coupling with NH protons; therefore, the tautomeric form **7** was assigned for these compounds. The signal of NH proton gave the cross-peaks with the signals of CH_2 and SMe protons in 2D NOESY spectra of the compounds. These findings together with the absence of cross-peaks between signals of CH_2 and SMe protons indicated that *E*-configuration (**7**) was preferred over *Z*-configuration (**7''**) for the isothioureas (**7**). The reaction of **7** with hydrazine afforded 3,5-diamino-1,2,4-triazoles (**8**). For the comparison purpose 1,2,4-triazole (**9**) was prepared analogously from **6**.



Scheme 2

Table 1. Synthesis of 3(5)-amino-1,2,4-triazoles.

Compound	*Method*	*Yield, %*	*Mp, ºC*	*Solvent*	*Mp, ºC [lit.]*
5a	A	74	173-174	water	170-170.5 [6]
5b	B	97	186-187	water	186-187 [7]
5c	B	98	272-274	water	273-274 [8]
8a	C	92	161-162	water	161-162 [9]
8b	C	94	151-152	2-PrOH	148-149 [9]
8c	C	89	118-119	water	117-119 [10]
9	D	75	138-139	2-PrOH	136-137 [11]

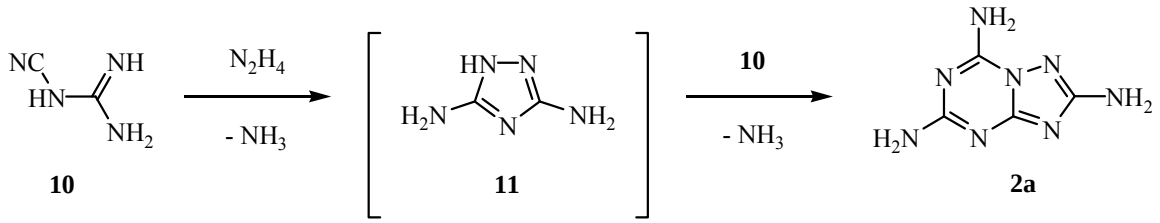
Table 2. NMR spectral data of 3(5)-amino-1,2,4-triazoles.

Compound	*^{1}H NMR (300 MHz, DMSO-d_6), δ*	*^{13}C NMR (75 MHz, DMSO-d_6), δ*
5a	3.73 (2H, s, CH_2), 5.12* and 5.81 (2H, 2 br.s, NH_2), 7.07-7.38 (5H, m, Ph), 11.66 and 12.49* (1H, 2 br.s, NH)	34.3 (CH_2), 125.9 (C-4'), 128.0 (C-2' and C-6'), 128.6 (C-3' and C-5'), 139.0 (C-1'), 156.9, 159.6 (C-3 and C-5)
5b	5.39* and 6.12 (2H, 2 br.s, NH_2), 7.28-7.52 (3H, m, H-3', H-4' and H-5'), 7.92 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 12.09 and 13.24* (1H, 2 br.s, NH)	126.3 (C-2' and C-6'), 128.1 (C-4'), 128.3 (C-3' and C-5'), 132.3 (C-1'), 157.3, 158.3 (C-3 and C-5)
5c	5.52* and 6.28 (2H, 2 br.s, NH_2), 7.81 (2H, dd, *J* = 4.9, 1.5 Hz, H-3' and H-5'), 8.62 (2H, dd, *J* = 4.9, 1.5 Hz, H-2' and H-6'), 12.40 and 13.69* (1H, 2 br.s, NH)	119.5 (C-3' and C-5'), 139.2 (C-4'), 149.9 (C-2' and C-6'), 156.4, 157.6 (C-3 and C-5)
8a	5.83 (2H, br.s, NH_2), 6.71 (1H, t, *J* = 7.2 Hz, H-4'), 7.15 (2H, t, *J* = 7.7 Hz, H-3' and H-5'), 7.49 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 8.58 (1H, s, NH), 11.12 (1H, br.s, N(1)H)	115.4 (C-2' and C-6'), 118.1 (C-4'), 128.3 (C-3' and C-5'), 142.5 (C-1'), 155.3, 157.8 (C-3 and C-5)
8b	4.23 (2H, d, *J* = 6.4 Hz, CH_2), 5.37 (2H, br.s, NH_2), 6.15 (1H, br.s, NH), 7.18 (1H, tt, *J* = 6.7, 1.9 Hz, H-4'), 7.23-7.34 (4H, m, H-2', H-3', H-5' and H-6')	46.1 (CH_2), 126.3 (C-4'), 127.0 (C-2' and C-6'), 127.9 (C-3' and C-5'), 140.9 (C-1'), 157.7, 160.0 (C-3 and C-5)
8c	2.78 (2H, t, *J* = 7.5 Hz, PhCH_2), 3.23 (2H, dt, *J* = 7.0, 7.5 Hz, NHCH_2), 5.27 (2H, br.s, NH_2), 5.56 (1H, br.s, NH), 7.15-7.32 (5H, m, Ph), 10.74 (1H, br.s, N(1)H)	35.5 (PhCH_2), 44.4 ($NHCH_2$), 125.8 (C-4'), 128.1 (C-2' and C-6'), 128.5 (C-3' and C-5'), 139.9 (C-1'), 158.1, 159.8 (C-3 and C-5)
9	2.42 (3H, s, SMe), 6.02 (2H, br.s, NH_2), 11.77 (1H, br.s, N(1)H)	13.5 (SMe), 156.3, 157.8 (C-3 and C-5)

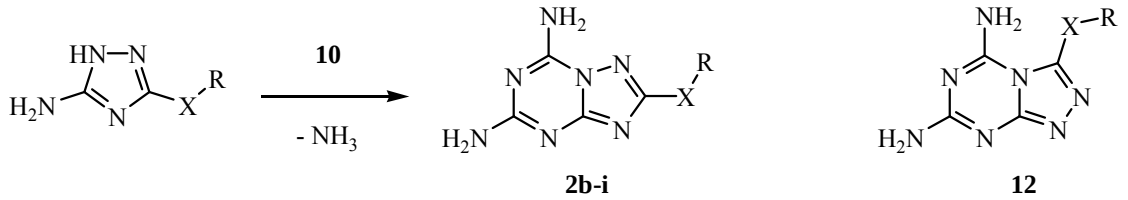
* signals of the minor tautomeric form 3-amino-1,2,4-triazoles

The previous reports on the reaction of 3(5)-amino-1,2,4-triazoles with cyanoguanidine (**10**) are controversial.[5] In order to provide conclusive results on the structure of the reaction products, for the comparison purpose, we decided to prepare 2,5,7-triamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazine (**2a**) which structure had been previously established using X-ray crystallography.[12] The reaction of cyanoguanidine (**10**) with hydrazine proceeded via guanazole (**11**) and afforded **2a** (Scheme 3). The (3+3) heterocyclization of 3(5)-amino-1,2,4-triazoles using **10** as C-N-C fragment introducing reagent was

successfully applied for the synthesis of 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2b-i**) (Scheme 4).



Scheme 3



Scheme 4

Table 3. Synthesis of 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2**).

Compound	*X*	*R*	*Method*	*Formula**	*Yield, %*	*Mp, ºC*	*Solvent*
2a	-	NH_2	A	$C_4H_6N_8$	65	> 360	DMF
2b	CH_2	Ph	B	$C_{11}H_{11}N_7$	52	342	DMF
2c	-	Ph	B	$C_{10}H_9N_7$	64	> 360	DMF
2d	-	4-Py	C	$C_9H_8N_8$	50	> 360	DMF
2e	NH	Ph	B	$C_{10}H_{10}N_8$	55	359-360	DMF
2f	$NHCH_2$	Ph	B	$C_{11}H_{12}N_8$	68	288-290	DMF / water
2g	$NHCH_2CH_2$	Ph	B	$C_{12}H_{14}N_8$	65	298	DMF / water
2h	S	Me	B	$C_5H_7N_7S$	57	> 360	DMF
2i	-	H	B	$C_4H_5N_7$	70	> 360	DMF

* satisfactory elemental analyses obtained (C ± 0.36, H ± 0.28, N ± 0.33)

The structures of the prepared 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2b-i**) were established using ^{1}H and ^{13}C NMR spectroscopic data (Tables 4, 5). The alternative isomeric structure of 1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**12**)[13] was excluded for the compounds obtained based on the following results. The 7-amino group of **2** appeared in the ^{1}H NMR spectra as one or two broad signals (Table 4). This observation can be explained by the coplanarity of the 7-amino group with the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus, stabilized with intramolecular hydrogen bonding N-H…N-1, and consequent deshielding of one of the amino group protons. This type of stabilization would not be possible in the case of [4,3-*a*] ring junction. The free energy of activation ($G^{\ddagger}$) of the rotation across (C7)-NH_2 bond at the coalescence temperature was estimated for **2h** using dynamic ^{1}H NMR spectroscopy. For this compound (**2h**) $G^{\ddagger}_{303}$ was found to be equal 63.8 kJ mol^{-1}. The results of ^{13}C NMR

spectroscopic study of the compounds (**2**) (Table 5) also confirmed the formation of 1,2,4-triazolo[1,5-*a*][1,3,5]triazine nucleus. The assignments were made based on the literature data[14-15] for related compounds as well as comparisons with 2-amino and methylthio substituted 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**2a,h**) and unsubstituted at position 2 of the heterocyclic core (**2i**).

Table 4. ^{1}H NMR spectra of 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (300 MHz, DMSO-d_6), δ.

Compound	*C(5)NH$_2$*	*C(7)NH$_2$*	*XR*
2a	6.91, s	8.23, br.s	8.07 (2H, s, NH_2)
2b	6.84, s	8.02 and 8.09 two br.s	3.96 (2H, s, CH_2), 7.16-7.35 (5H, m, Ph)
2c	6.96, s	8.07 and 8.27, two br.s	7.45-7.58 (3H, m, H-3', H-4' and H-5'), 8.12 (2H, d, *J* = 7.5 Hz, H-2' and H-6')
2d	7.03, s	8.15 and 8.36, two br.s	7.99 (2H, dd, *J* = 4.5, 1.3 Hz, H-3' and H-5'), 8.74 (2H, dd, *J* = 4.9, 1.5 Hz, H-2' and H-6')
2e	6.77, s	7.83, br.s	9.45 (1H, s, NH), 6.86 (1H, t, *J* = 7.4 Hz, H-4'), 7.25 (2H, t, *J* = 7.9 Hz, H-3' and H-5'), 7.73 (2H, d, *J* = 7.9 Hz, H-2' and H-6')
2f	6.62, s	7.67, br.s	4.41 (2H, d, *J* = 6.6 Hz, CH_2), 6.62, (1H, t, *J* = 6.6 Hz, NH), 7.21 (1H, t, *J* = 7.0 Hz, H-4'), 7.26-7.39 (4H, m, H-2', H-3', H-5' and H-6')
2g	6.61, s	7.55, br.s	2.86 (2H, t, *J* = 7.3 Hz, PhCH_2), 3.39 (2H, dt, *J* = 7.3, 7.2 Hz, NHCH_2), 6.46, (1H, t, *J* = 5.7 Hz, NH), 7.16-7.33 (5H, m, Ph)
2h	6.92, s	7.88 and 8.17, two br.s	2.57 (3H, s, SMe)
2i	6.58, s	7.51, br.s	5.79 (1H, s, H-2)

Table 5. ^{13}C NMR spectra of 5,7-diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (75 MHz, DMSO-d_6), δ.

Compound	*C-2*	*C-3a*	*C-5*	*C-7*	*X*	*R*
2a	165.3	158.5	162.1	149.4	-	-
2b	165.3	159.3	162.5	150.2	34.7	126.2 (C-4'), 128.2 (C-2' and C-6'), 128.7 (C-3' and C-5'), 137.8 (C-1')
2c	162.7	159.5	162.6	150.4	-	126.6 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.9 (C-4'), 130.8 (C-1')
2d	160.7	159.7	162.7	150.4	-	120.6 (C-3' and C-5'), 138.0 (C-4'), 150.3 (C-2' and C-6')
2e	161.4	157.5	162.5	149.7	-	116.6 (C-2' and C-6'), 119.8 (C-4'), 128.5 (C-3' and C-5'), 141.0 (C-1')
2f	165.5	158.5	162.2	149.4	45.4	126.4 (C-4'), 127.0 (C-2' and C-6'), 128.0 (C-3' and C-5'), 140.5 (C-1')
2g	165.3	158.4	162.2	149.4	35.2, 43.9	125.8 (C-4'), 128.1 (C-2' and C-6'), 128.6 (C-3' and C-5'), 139.8 (C-1')
2h	165.1	159.3	162.5	149.6	-	13.1
2i	154.0	158.8	162.2	150.6	-	-

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{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.

(Het)arylamidoguanidines (4b,c) were prepared from hydrazides (**3b,c**) using the reported method.[7] **4b:** Yield 86%, mp 176ºC, [lit.,[7] mp 184ºC]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (2H, br. s, NH_2), 7.16 (2H, br. s, NH_2), 7.29 (3H, m, $W_{1/2}$ = 9 Hz, H-3, H-4 and H-5), 7.95 (2H, m, $W_{1/2}$ = 12 Hz, H-2 and H-6), 11.01 (1H, br. s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 126.5 (C-3 and C-5), 127.3 (C-2 and C-6), 128.0 (C-4), 138.5 (C-1), 152.9 (N=$C(NH_2)_2$), 160.5 (C=O). **4c:** Yield 76%, mp 270-271ºC, [lit.,[16] mp 272ºC]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (2H, s, NH_2), 7.08 (2H, s, NH_2), 7.84 (2H, dd, J = 4.5, 1.5 Hz, H-3 and H-5), 8.50 (2H, dd, J = 4.5, 1.5 Hz, H-2 and H-6), 10.66 (1H, br. s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 121.1 (C-3 and C-5), 146.0 (C-4), 149.0 (C-2 and C-6), 152.9 (N=$C(NH_2)_2$), 158.7 (C=O).

***N*-Substituted *N'*-cyano-*S*-methylisothioureas (7)** were prepared using the reported method.[17] **7a:** Yield 85%, mp 198-200ºC (MeOH), [lit.,[18] mp 199-200°C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.70 (3H, s, SMe), 7.25 (1H, tt, J = 6.8, 1.8 Hz, H-4'), 7.36-7.48 (4H, m, Ph), 10.16 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.7 (SMe), 114.7 (CN), 124.1 (C-2 and C-6), 123.3 (C-4), 128.7 (C-3 and C-5), 137.1 (C-1), 170.2 (N=*C*(SMe)N). **7b:** Yield 88%, mp 159-161ºC (MeOH), [lit.,[17] mp 157-158°C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.62 (3H, s, SMe), 4.49 (2H, s, CH_2), 7.23-7.40 (5H, m, Ph), 8.89 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.0 (SMe), 46.1 (CH_2), 115.6 (CN), 127.1 (C-4), 127.2 (C-2 and C-6), 128.3 (C-3 and C-5), 137.4 (C-1), 170.2 (N=*C*(SMe)N). **7c:** Yield 90%, mp 174ºC (MeOH), [lit.,[19] mp 172-175°C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.52 (3H, s, SMe), 2.83 (2H, t, J = 7.3 Hz, PhCH_2), 3.50 (2H, t, J = 7.3 Hz, NCH_2), 7.19-7.35 (5H, m, Ph), 8.42 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9 (SMe), 33.9 (Ph*C*H_2), 44.3 (NCH_2), 115.8 (CN), 126.3 (C-4), 128.3 (C-2 and C-6), 128.7 (C-3 and C-5), 138.5 (C-1), 169.7 (N=*C*(SMe)N).

3(5)-Amino-1,2,4-triazoles. *Method A.* To a stirred solution of *S*-methylisothiourea sulfate (2.8 g, 10 mmol) in 20 mL 1M NaOH, penylacetylhydrazide (**3a**, 3.0 g, 20 mmol) was added at 0ºC, the stirring was continued at rt for 48 h and then for 3 h at 50ºC. After cooling, the precipitated **5a** was filtered, washed with ice-cold water and recrystallized from water. *Method B.* (Het)arylamidoguanidines (**4b,c**, 20 mmol) were heated under reflux in 15 mL of water for 3-5 h. After cooling, the precipitated **5b,c** were filtered, washed with ice-cold water and dried. After recrystallization from water mp of the compounds did not change. *Method C.* To a stirred suspension of **7** (10 mmol) in 15 mL of EtOH, hydrazine hydrate (98%, 1.0 mL, 20 mmol) was added dropwise at rt within 5 min. The reaction mixture was heated under reflux for 3 h, the solvent was removed under vacuum and the solid obtained was recrystallized to give **8**. *Method D.* To a stirred solution of **6** (5.8 g, 40 mmol) in 20 mL of MeOH hydrazine hydrate (98%, 2.2 mL, 44 mmol) was added dropwise at rt within 5 min. The reaction mixture was heated at 40°C for 5 h,

the solvent was removed under vacuum and the solid was recrystallized from *i*-PrOH to give **9**.

5,7-Diamino[1,2,4]triazolo[1,5-*a*][1,3,5]triazines (2). *Method A.* **2a** was prepared using the reported method.[13] *Method B.* To a stirred solution of appropriate 3(5)-amino-1,2,4-triazole (5 mmol) and 0.5 mL (5 mmol) of conc. HCl in 10 mL of water, cyanoguanidine (**10**, 0.5 g, 6 mmol) was added and the solution was heated under reflux for 7-24 h. After cooling, the product was filtered, washed with water and recrystallized. *Method C.* To a stirred solution of **5c** (0.8 g, 5 mmol) in 5 mL of DMF cyanoguanidine (**10**, 0.5 g, 6 mmol) of was added and the resulting solution was heated under reflux for 4 h. After cooling, the product (**2d**) was filtered, washed with EtOH and recrystallized from DMF.

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