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A SIMPLE SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 1,2,4-TRIAZOLOPYRIMIDINE DERIVATIVES

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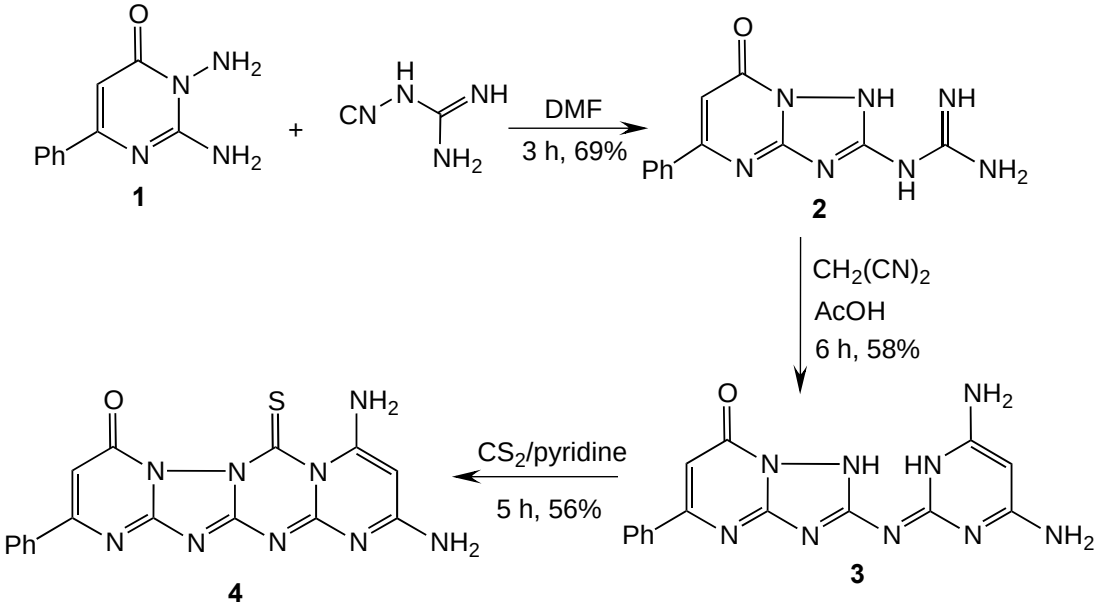
Abstract – The synthesis of new 1-(7-oxo-5-phenyl-1,7-dihydro[1,2,4]triazolo-[1,5-*a*]pyrimidin-2-yl)guanidine (**2**) by reaction 2,3-diamino-6-phenylpyrimidin-4(3*H*)-one (**1**) with cyanoguanidine was achieved. Compound **2** reacted with malononitrile to produce diaminopyrimidine derivative **3** which upon treatment with CS_2 resulted in the formation of 1,3,5-triazine **4**. Cyclization of compound **1** with either benz[*c*]acridine-7-carboxylic acid or mandelic acid in presence of phosphoryl chloride was investigated. Moreover, 2-[chloro(phenyl)methyl]-5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7(1*H*)-one (**6**) was used as a valuable scaffold to construct various fused and attached heterocyclic rings *via* simple reactions. The antimicrobial activity of the synthesized compounds were tested. Spectral and analytical data of the newly synthesized compounds were all in good agreement with the proposed chemical structures.

In recent years, triazoles and pyrimidines have attracted attention due to their biological and chemotherapeutic activities. 1,2,4-Triazoles play important role in the medicinal chemistry due to their biological activities.[1] In addition, the ring system of 1,2,4-triazolopyrimidines is isoelectronic with that of purines.[2,3] 1,2,4-Triazolopyrimidines have aroused increasing attention from the chemical and biological view points, due to their diverse range of biological activities, such as antitumor potency,[4-8] antimalarial,[9] antimicrobial,[10-13] anticancer,[14] anti-inflammatory[15] inhibition of KDR kinase,[16] antifungal effect,[17] macrophage activation,[18] anxiolytic[19] and antileukemia agents.[20-22] Interestingly, the first 1,2,4-triazolopyrimidine antibiotic essramycin has been isolated from natural sources.[23] In continuation of the work directed to synthesis of pyrimidine heterocyclic compounds,[24,25] we herein report an efficient

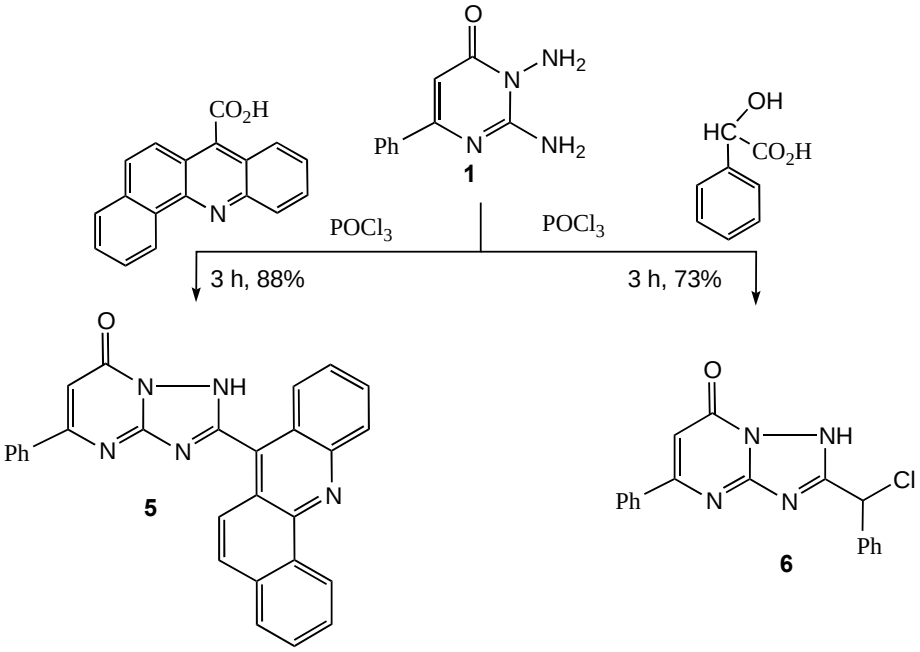
synthesis of some new 1,2,4-triazolopyrimidines from 2,3-diamino-6-phenylpyrimidin-4(3*H*)-one in relatively good yields and evaluated them for their antimicrobial activity.

The synthesis of (1,2,4-triazolo[1,5-*a*]pyrimidinyl)guanidine **2** from 2,3-diamino-6-phenylpyrimidin-4(3*H*)-one (**1**)[26] was examined using cyanoguanidine in DMF. Moreover, treatment of compound **2** with malononitrile in glacial acetic acid afforded 1,2,4-triazolo[1,5-*a*]pyrimidine **3**, which in turn reacted with carbon disulfide in pyridine to give 1,3,5-triazine **4** (Scheme 1). The mass spectrum of compound **2** recorded the molecular ion peak at *m/z* 269 which agrees with the suggested molecular formula $C_{12}H_{11}N_7O$. The ^{1}H NMR spectrum of compound **3** revealed two D_2O-exchangeable signals at δ 3.80 and 4.40 due to two NH_2 protons in addition to two D_2O-exchangeable signal at δ 8.50 and 8.70 corresponding to NH protons. The ^{1}H NMR spectrum of compound **4** revealed the absence of NH signals. Its mass spectrum represent a good evidence for structure of compound **4** and showed the molecular ion peak at *m/z* 377 with a base peak at 57.



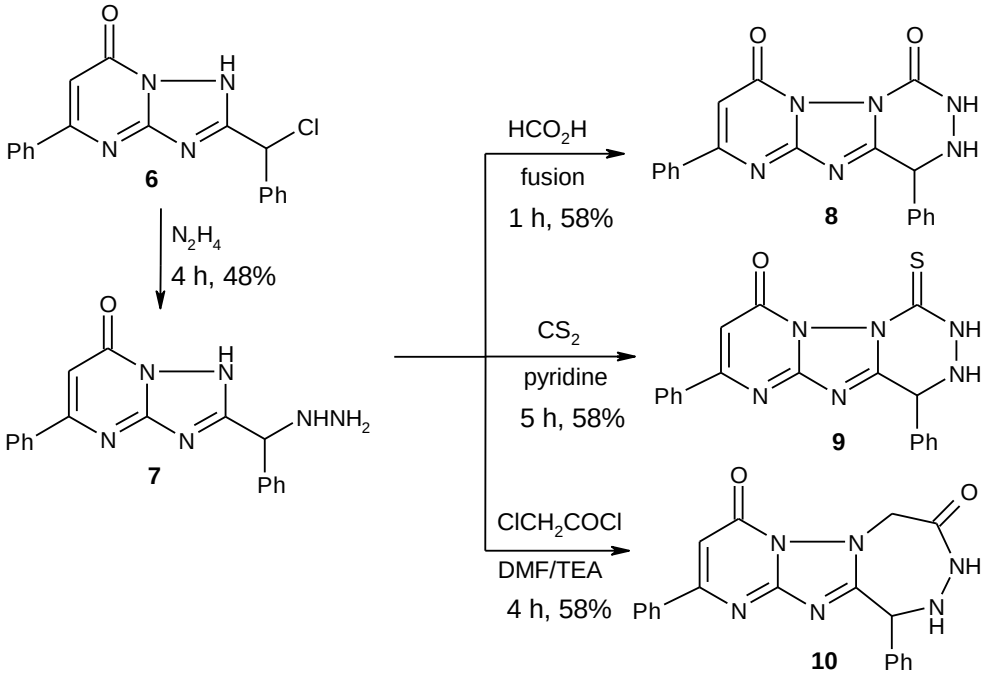
Scheme 1. Synthesis of triazolopyrimidinyl-guanidine **2**, -pyrimidine **3** and -triazine **4**

Also, upon the fact that phosphoryl chloride consider as a good cyclizing agent, therefore, reaction of compound **1** with carboxylic acid derivatives was studied. Thus, reaction of compound **1** with either benz[*c*]acridine-7-carboxylic acid or mandelic acid in presence of phosphoryl chloride gave triazolopyrimidines **5** and **6**, respectively, (Scheme 2). The IR spectra of compounds **5** and **6** lacked an absorption bands corresponding to NH_2 groups. The mass spectrum of compound **6** showed a base peak at *m/z* 77 which is attributed to phenyl group.



Scheme 2. Synthetic route for preparation of triazolopyrimidines **5** and **6**

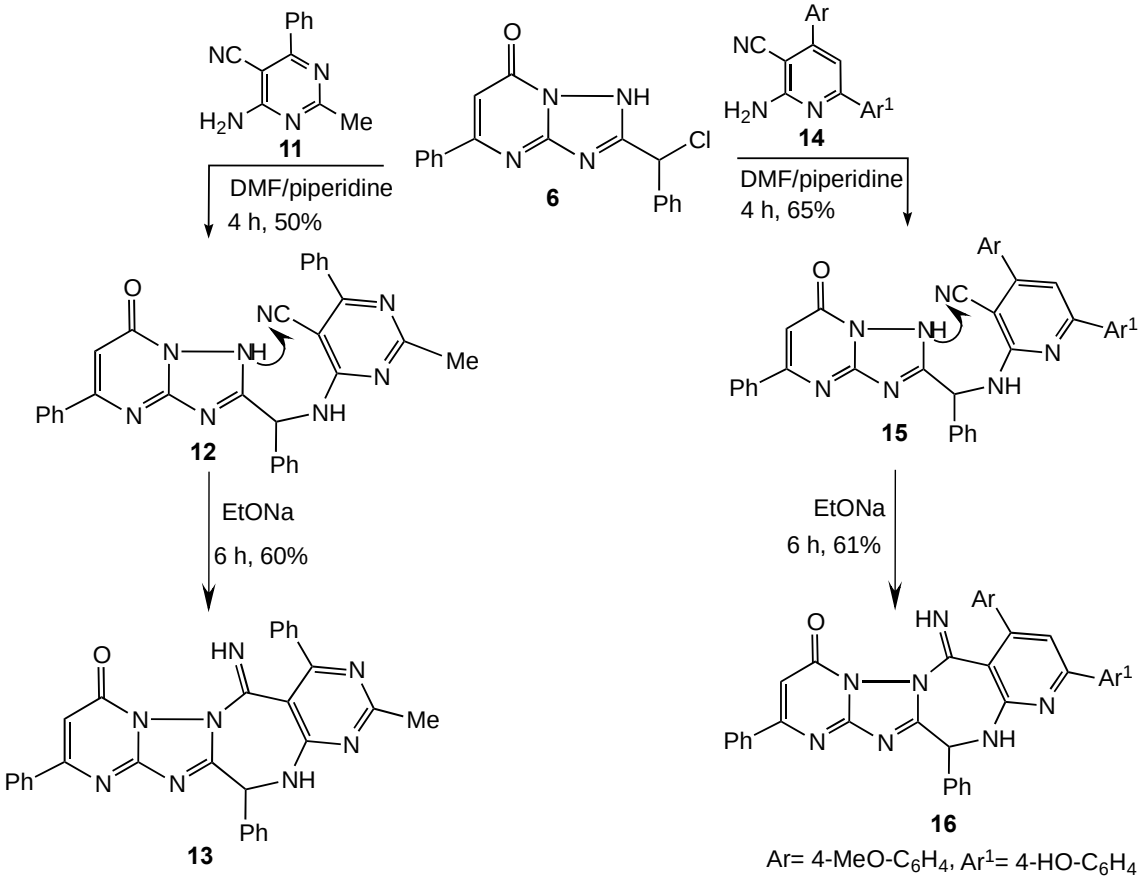
On the other hand, reaction of compound **6** with hydrazine hydrate afforded the hydrazino derivative **7**. Further, cyclocondensation reaction of compound **7** with some electrophiles, namely, formic acid, carbon disulfide and chloroacetyl chloride led to the formation of triazines **8**, **9** and triazepine **10**, respectively, (Scheme 3). The ^{13}C NMR spectrum of compound **7** showed characteristic signals at δ 97.2 and 158 assigned the – CHPh and C=O carbons, respectively.



Scheme 3. Synthesis of hydrazino derivative **7**, triazines **8**, **9** and triazepine **10**

The mass spectra of compounds **7**, **8**, **9** and **10** recorded their molecular ion peak at *m/z* 332, 358, 374 and 372 corresponding to their formula weights $C_{18}H_{16}N_6O$, $C_{19}H_{14}N_6O_2$, $C_{19}H_{14}N_6OS$ and $C_{20}H_{16}N_6O_2$, respectively. The mass spectra of compounds **7**, **8** and **9** exhibited a base peak at *m/z* 77 which is attributed to phenyl group, while, compound **10** showed a peak at *m/z* 77 (99.7%) which is attributed to phenyl group with a base peak at *m/z* 57 corresponding to [O=CNHN$^+$]. The ^{13}C NMR spectrum of compound **9** revealed characteristic signals at δ 86.9, 155.8 and 186 attributed to the - CHPh, C=O and C=S carbons, respectively.

Interaction of compound **7** with heterocyclic compounds having vicinal amino and cyano functions afforded novel polynuclear heterocyclic system. Thus, treatment of compound **7** with 4-amino-2-methyl-6-phenylpyrimidine-5-carbonitrile (**11**)[27] and/or 2-amino-6-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-pyridine-3-carbonitrile (**14**)[28] in boiling DMF containing few drops of piperidine gave pyrimidine-5-carbonitrile **12** and pyridine-3-carbonitrile **15**, respectively. Compounds **12** and **15** were heated in sodium ethoxide to yield diazepines **13** and **16**, respectively, (Scheme 4). The recorded absorption bands in the region of 2218 and 2205 cm^{-1} in the IR spectra of compounds **12** and **15** were assignable to CN group, respectively.



Scheme 4. Formation of pyrimidine **12**, pyridine **15**, diazepine **13** and **16**

The IR spectra of **13** and **16** lacked an absorption corresponding to CN group. The ^{1}H NMR spectra showed signals in the region of δ 5.90, 5.85, 5.80 and 5.82 ppm corresponding to CH-methine protons in **12**, **13**, **15** and **16**, respectively. The ^{13}C NMR spectrum of compound **12** showed characteristic signals at δ 83.6, 116.1 and 169.1 attributed to –CHPh, CN and C=O carbons, respectively. The ^{1}H NMR spectra of compounds **15** and **16** revealed characteristic signals at δ 7.61/7.97/9.90 and 7.58/7.85/10.10 ppm attributed to pyridine-H, pyrimidine-H and OH protons, respectively.

The *in vitro* antimicrobial activity of the newly synthesized compounds against *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922) as examples of Gram negative bacteria, *Bacillus subtilis* (ATCC-6635) and *Staphylococcus aureus* (ATCC 25923) as examples of Gram positive bacteria, *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* as fungal strains was investigated using the disk diffusion method.[29] In general, most of the prepared compounds showed antifungal activity better than antibacterial activity. Compounds **13** and **16** showed good inhibitions against fungal strains. This activity may be attributed to the presence of the formed bioactive diazepine ring. The results are given in Table 1.

Table 1. The antimicrobial activity of the newly synthesized compounds

	Diameter of inhibition zone[a] *(mm), Conc. (100 µg mL^{-1})*					
	Gram - positive bacteria		**Gram - negative bacteria**		**Yeasts and Fungi**	
Compd No.	*Staphylococcus aureus* (ATCC 25923)	*Bacillus subtilis* (ATCC 6635)	*Salmonella typhimurium* (ATCC 14028)	*Escherichia coli* (ATCC 25922)	*Candida albicans* (ATCC 10231)	*Aspergillus fumigatus*
2	-	10	12	17	19	-
3	-	7	8	9	17	-
4	-	18	14	16	-	-
5	-	-	10	7	-	-
6	-	10	11	12	14	-
7	-	11	-	-	13	7
8	-	10	-	10	13	11
9	-	12	-	13	14	11
10	-	-	-	-	11	-
12	-	11	-	9	16	10
13	-	14	-	10	24	8
15	-	-	-	8	18	7
16	-	-	17	8	26	7
Control[b]	**35**	**35**	**36**	**38**	**35**	**37**

[a]12 mm or less: resistant or no inhibition, 13–19 mm: moderate inhibition, 20 mm or more: strong inhibition. [b]Chloramphencol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria, Fluconazolein in the case of yeasts and Cycloheximide in the case of fungi.

In summary, 2,3-diamino-6-phenylpyrimidin-4(3*H*)-one (**1**) has proved to be a versatile precursor and readily accessible building block for the synthesis of some novel triazolopyrimidine derivatives. Some of the synthesized compounds showed a low to high antimicrobial activity towards Gram positive bacteria, Gram negative bacteria and the fungal strains. All these derivatives were characterized by analytical and spectroscopic data.

EXPERIMENTAL

All the reported melting points were uncorrected. The IR spectra were recorded on FT-IR Jasco 4100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. Elemental microanalyses were recorded on a Perkin Elmer series II CHNS analyzer 2400. Mass spectra were obtained using gas chromatography GCMS qp-2010 and on a Shimadzu instrument mass spectrometer (70 eV). The purity of the synthesized compounds was checked by thin layer chromatography (TLC). 3-Diamino-6-phenylpyrimidin-4(3*H*)-one (**1**),[26] 4-amino-2-methyl-6-phenyl-pyrimidine-5-carbonitrile (**12**),[27] and 2-amino-6-(4-hydroxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (**15**)[28] were prepared according to the published methods.

1-(7-Oxo-5-phenyl-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)guanidine (2). A mixture of compound **1** (0.202 g, 1 mmol) and cyanoguanidine (0.084 g, 1 mmol) in DMF (5 mL) was heated under reflux for 3 h. After cooling, pour onto ice and dil. HCl. The solid obtained was filtered off and recrystallized from MeOH to give compound **2** as brown crystals (0.185 g, 69%): mp 195-197 ºC; IR (ν cm^{-1}) 3314-3161 (3NH, NH_2), 3020 ($CH_{arom.}$), 1655 (C=O), 1600 (C=N), 1583 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.47 (brs, 2H, NH_2 exchangeable with D_2O), 6.24 (s, 1H, NH exchangeable with D_2O), 6.50 (s, 1H, NH exchangeable with D_2O), 6.81-8.24 (m, 5H, Ar-H), 8.38 (s, 1H, H-6$_{pyrimidinone}$), 12 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 120.4, 126.6, 127.3, 128.2, 128.5, 128.7, 129.4, 130.1, 130.7, 131.9, 147.2, 165.3 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 269 (1.5), [M+1] 270 (1), [M+2] 271 (1.4), 256 (3.1), 212 (18.7), 202 (12.4), 129 (16.5), 77 (43.4), 57 (100); Anal. Calcd for $C_{12}H_{11}N_7O$ (%): C, 53.53; H, 4.12; N, 36.41. Found: C, 53.60; H, 4.10; N, 36.40%.

2-{[4,6-Diaminopyrimidin-2(1*H*)-ylidene]amino}-5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-(1*H*)-one (3). A mixture of compound **2** (0.269 g, 1 mmol), malononitrile (0.066 g, 1 mmol) in glacial acetic acid (5 mL) was heated under reflux for 6 h. After cooling, pour onto H_2O. The solid obtained was collected and recrystallized from EtOH to give compound **3** as pale brown crystals (0.194 g, 58%): mp 214-216 ºC; IR (ν cm^{-1}) 3350-3161 (2NH, 2NH_2), 3050 ($CH_{arom.}$), 1651 (C=O), 1600 (C=N), 1550 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 2H, NH_2 exchangeable with D_2O), 4.40 (s, 2H, NH_2 exchangeable with D_2O), 6.49 (s, 1H, H-5$_{pyrimidine}$), 7.45-8.08 (m, 5H, Ar-H), 8.36 (s, 1H, H-6$_{pyrimidinone}$), 8.50 (s, 1H, NH

exchangeable with D_2O), 8.70 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 124.2, 126.4, 128.8, 129, 129.6, 129.8, 131.2, 131.9, 144.2, 145, 146.9, 165.4 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 335 (0.3), [M+1] 336 (0.3), [M+2] 337 (0.6), 275 (8.7), 239 (32.5), 129 (15.3), 91 (6.4), 77 (10.5), 57 (100); Anal. Calcd for $C_{15}H_{13}N_9O$ (%): C, 53.73; H, 3.91; N, 37.59. Found: C, 53.70; H, 3.90; N, 37.58%.

9,11-Diamino-2-phenyl-7-thioxo-4*H*-pyrimido[1,2-*a*]pyrimido[1',2':2,3][1,2,4]triazolo[5,1-*d*][1,3,5]-triazin-4-one (4). A mixture of compound **3** (0.335 g, 1 mmol) and carbon disulfide (0.2 mL) in pyridine (5 mL) was refluxed for 5 h. The reaction mixture was left to cool and poured onto ice and dil. HCl. The solid obtained was filtered off and washed with H_2O and recrystallized from EtOH to give compound **4** as pale brown crystals (0.211 g, 56%): mp 218-220 ºC; IR (ν cm^{-1}) 3250, 3230 ($2NH_2$), 3010 ($CH_{arom.}$), 1680 (C=O), 1635 (C=N), 1600 (C=C), 1220 (C=S); ^1H NMR (300 MHz, DMSO-d_6) δ 4.10 (brs, 2H, NH_2 exchangeable with D_2O), 6.28 (brs, 2H, NH_2 exchangeable with D_2O), 6.80 (s, 1H, H-$10_{pyrimidine}$), 7.47-8.47 (m, 5H, Ar-H), 9.01 (s, 1H, H-$3_{pyrimidinone}$); ^{13}C NMR (75 MHz) δ 126.6, 126.9, 127.4, 128.6, 128.7, 129.2, 130.2, 130.9, 142.6, 144.9, 158.3 (C=O), 178 (C=S); MS *m/z* (%): $[M]^{\cdot+}$ 377 (1.1), [M+1] 378 (1.1), [M+2] 379 (1), 316 (29.1), 226 (44), 212 (33.6), 129 (26.6), 91 (17), 77 (99.8), 57 (100); Anal. Calcd for $C_{16}H_{11}N_9OS$ (%): C, 50.92; H, 2.94; N, 33.40; S, 8.50. Found: C, 50.90; H, 2.92; N, 33.44; S, 8.52%.

2-Acridin-7-yl-5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7(1*H*)-one (5). A mixture of compound **1** (0.202 g, 1 mmol) and benz[*c*]acridine-7-carboxylic acid (0.273 g, 1 mmol) in $POCl_3$ (3 mL) was heated for 3 h on water-bath. After cooling, pour onto ice and H_2O the solid obtained was filtered off and recrystallized from EtOH to give compound **5** as brown crystals (0.386 g, 88%): mp 132-134 ºC; IR (ν cm^{-1}) 3326 (NH), 3030 ($CH_{arom.}$), 1683 (C=O), 1646 (C=N), 1604 (C=C); ^1H NMR (DMSO-d_6) δ 7.13 (s, 1H, NH exchangeable with D_2O), 7.30-8.48 (m, 15H, Ar-H and H-$6_{pyrimidinone}$). ^{13}C NMR (75 MHz) δ 120.4, 121.6, 121.8, 122, 122.4, 123.7, 124.4, 124.8, 125.2, 125.6, 125.8, 126.2, 128.6, 129.2, 129.4, 129.8, 131.6, 132, 142.8, 143.6, 144.2, 144.4, 146.8, 170.2 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 439 (0.12), [M+1] 440 (0.11), 275 (100), 230 (76.2), 202 (16.6), 129 (9.7), 114 (35.8), 77 (14.7), 57 (17.1); Anal. Calcd for $C_{28}H_{17}N_5O$ (%): C, 76.52; H, 3.90; N, 15.94. Found: C, 76.50; H, 3.90; N, 15.90%.

2-[Chloro(phenyl)methyl]-5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7(1*H*)-one (6). A mixture of compound **1** (0.202 g, 1 mmol) and mandelic acid (0.152 g, 1 mmol) was heated under reflux for 3 h in $POCl_3$ (3 mL). After cooling, pour onto ice and H_2O the solid obtained was collected and recrystallized from MeOH to give compound **6** as brown crystals (0.245 g, 73%): mp 128-130 ºC; IR (ν cm^{-1}) 3230 (NH), 3061 ($CH_{arom.}$), 2924 ($CH_{aliph.}$), 1682 (C=O), 1624 (C=N), 1559 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ 5.74 (s, 1H, $CH_{methine}$), 7.28-8.01 (m, 10 H, Ar-H), 8.04 (s, 1H, H-$6_{pyrimidinone}$), 11.10 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 98.8 (-**C**HPh), 122.4, 124.9, 126.2, 126.6, 126.9, 127, 127.6, 127.9, 128.2, 128.6, 128.8, 132.7, 138.4, 139.6, 160 (C=O). MS *m/z* (%): $[M]^{\cdot+}$ 336 (2.4), [M+1]

337 (1), [M+2] 338 (0.8), 229 (22.5), 202 (21.4), 129 (13), 91 (59.8), 77 (100), 57 (52.8); Anal. Calcd for $C_{18}H_{13}ClN_4O$ (%): C, 64.19; H, 3.89; N, 16.64. Found: C, 64.20; H, 3.90; N, 16.60%.

2-[Hydrazino(phenyl)methyl]-5-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7(1*H*)-one (7). A mixture of compound **6** (0.336 g, 1 mmol) in DMF (5 mL) containing excess hydrazine hydrate (2 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **7** as brown crystals (0.159 g, 48%): mp 161-163 ºC; IR (ν cm^{-1}) 3350-3192 (2NH, NH_2), 3050 ($CH_{arom.}$), 2927 ($CH_{aliph.}$), 1680 (C=O), 1624 (C=N), 1600 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.11 (brs, 2H, NH_2 exchangeable with D_2O), 5.90 (s, 1H, $CH_{methine}$), 6.30 (s, 1H, NH exchangeable with D_2O), 7.21-7.89 (m, 10H, Ar-H), 8.05 (s, 1H, H-$6_{pyrimidinone}$), 8.80 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 97.2 (-**C**HPh), 120.4, 124.9, 126.2, 126.4, 126.7, 127.2, 127.4, 127.7, 128.2, 128.3, 128.6, 128.7, 128.9, 130.6, 158 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 332 (1.1), [M+1] 333 (0.9), [M+2] 334 (0.9), 302 (66.4), 275 (22.4), 226 (41.8), 129 (40.2), 91 (56.2), 77 (100), 57 (93.8); Anal. Calcd for $C_{18}H_{16}N_6O$ (%): C, 65.05; H, 4.85; N, 25.29. Found: C, 65; H, 4.86; N, 25.30%.

2,10-Diphenyl-9,10-dihydro-4*H*-pyrimido[1',2':2,3][1,2,4]triazolo[1,5-*d*][1,2,4]triazine-4,7(8*H*)-dione (8). A mixture of compound **7** (0.332 g, 1 mmol) and formic acid (3 mL) was fused for 1 h. The reaction mixture was cooled and triturated with MeOH. The solid obtained was filtered off and recrystallized from EtOH to give compound **8** as brown crystals (0.207 g, 58%): mp >300 ºC; IR (ν cm^{-1}) 3270-3220 (2NH), 3059 ($CH_{arom.}$), 2923 ($CH_{aliph.}$), 1683 (2C=O), 1623 (C=N), 1540 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.32 (s, 1H, $CH_{methine}$), 7.22 (s, 1H, NH exchangeable with D_2O), 7.26-7.80 (m, 10 H, Ar-H), 8.10 (s, 1H, H-$3_{pyrimidinone}$), 10.40 ppm (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 84.8 (-**C**HPh), 120.4, 122.6, 122.9, 124.6, 125.8, 126.2, 127.4, 128.2, 128.8, 129.6, 130.2, 136.2, 137.4, 137.8, 154.4, 156.8 (2 C=O); MS *m/z* (%): $[M]^{\cdot+}$ 358 (1), 302 (99.4), 288 (12.6), 237 (23.1), 199 (4.1), 129 (35.5), 91 (50.2), 77 (100), 57 (91.1); Anal. Calcd for $C_{19}H_{14}N_6O_2$ (%): C, 63.68; H, 3.94; N, 23.45. Found: C, 63.66; H, 3.92; N, 23.40%.

2,10-Diphenyl-7-thioxo-7,8,9,10-tetrahydro-4*H*-pyrimido[1',2':2,3][1,2,4]triazolo[1,5-*d*][1,2,4]-triazin-4-one (9). A mixture of compound **7** (0.332 g, 1 mmol) and carbon disulfide (0.2 mL) in pyridine (5 mL) was heated under reflux for 5 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained after neutralization with dil. HCl was filtered off and recrystallized from MeOH to give compound **9** as brown crystals (0.217 g, 58%): mp 152-154 ºC; IR (ν cm^{-1}) 3275-3150 (2NH), 3058 ($CH_{arom.}$), 2922 ($CH_{aliph.}$), 1692 (C=O), 1618 (C=N), 1589 (C=C), 1239 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 1H, $CH_{methine}$), 7.21-7.87 (m, 10H, Ar-H), 8.02 (s, 1H, NH exchangeable with D_2O), 8.10 (s, 1H, NH exchangeable with D_2O), 8.58 (s, 1H, H-$3_{pyrimidinone}$); ^{13}C NMR (75 MHz) δ 86.9 (-**C**HPh), 120.5, 123.7, 124.9, 125.6, 126.5, 127.2, 127.5, 128.6, 128.9, 129.9, 130.7, 136.1, 137.5,

137.8, 155.8 (C=O), 186 (C=S); MS *m/z* (%): $[M]^{\cdot+}$ 374 (0.5), [M+1] 375 (0.7), 348 (6.3), 302 (75.5), 226 (23.1), 129 (31.3), 91 (57), 77 (100), 57 (46.1); Anal. Calcd for $C_{19}H_{14}N_6OS$ (%): C, 60.95; H, 3.77; N, 22.45; S, 8.56. Found: C, 60.96; H, 3.78; N, 22.42; S, 8.54%.

2,11-Diphenyl-10,11-dihydropyrimido[1',2':2,3][1,2,4]triazolo[5,1-*d*][1,2,5]triazepine-4,8(7*H*,9*H*)-dione (10). A mixture of compound **7** (0.332 g, 1 mmol) and chloroacetyl chloride (0.1 mL) in DMF (5 mL) containing 2 drops of TEA was refluxed for 4 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from MeOH to give compound **10** as brown crystals (0.223 g, 60%): mp 134-136 ºC; IR (ν cm^{-1}) 3320-3200 (2NH), 3058 ($CH_{arom.}$), 2924 ($CH_{aliph.}$), 1663 (2C=O), 1600 (C=N), 1580 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.08 (s, 2H, CH_2CO), 6.20 (s, 1H, $CH_{methine}$), 6.80 (s, 1H, NH exchangeable with D_2O), 7.22-7.95 (m, 10 H, Ar-H), 8.05 (s, 1H, NH exchangeable with D_2O), 8.08 (s, 1H, H-3$_{pyrimidinone}$); ^{13}C NMR (75 MHz) δ 94.8 (-**C**HPh), 48.2 (**C**H_2), 122.2, 122.6, 123, 124.8, 125.4, 126.6, 127.2, 128.2, 128.6, 129.8, 134.2, 136.4, 137.8, 139.8, 158.2, 160.4 (2 C=O). MS *m/z* (%): $[M]^{\cdot+}$ 372 (1.8), [M+1] 373 (3.8), [M+2] 374 (2.1), 301 (81.3), 226 (16.9), 129 (43.5), 91 (72.7), 77 (99.7), 57 (100); Anal. Calcd for $C_{20}H_{16}N_6O_2$ (%): C, 64.51; H, 4.33; N, 22.57. Found: C, 64.50; H, 4.32; N, 22.56%.

2-Methyl-4-{[(7-oxo-5-phenyl-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)(phenyl)methyl]-amino}-6-phenylpyrimidine-5-carbonitrile (12). A mixture of compound **6** (0.336 g, 1 mmol) and 4-amino-2-methyl-6-phenylpyrimidine-5-carbonitrile (**11**) (0.210 g, 1 mmol) in DMF (5 mL) containing few drops of piperidine was heated under reflux for 4 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from MeOH to give compound **12** as brown crystals (0.255 g, 50%): mp 230-232 ºC; IR (ν cm^{-1}) 3380, 3151 (2NH), 3020 ($CH_{arom.}$), 2970 ($CH_{aliph.}$), 2218 (C≡N), 1678 (C=O), 1600 (C=N), 1544 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.20 (s, 3H, CH_3), 5.90 (s, 1H, $CH_{methine}$), 7.50-7.56 (m, 10 H, Ar-H), 7.72 (s, 2H, 2NH exchangeable with D_2O), 7.82-7.85 (m, 5 H, Ar-H), 8.20 (s, 1H, H-6$_{pyrimidinone}$); ^{13}C NMR (75 MHz) δ 25.8 (CH_3), 83.6 (-**C**HPh), 116.1 (CN), 120.4, 121.8, 122.6, 123.2, 124.9, 125, 126.4, 126.6, 127.2, 127.4, 127.7, 128, 128.2, 128.3, 129, 130.5, 134, 136.3, 169.1 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 510 (0.4), [M+1] 511 (0.2), [M+2] 512 (0.1), 302 (6.9), 287 (100), 272 (24.7), 129 (23.3), 91 (17.4), 77 (47.8), 57 (71); Anal. Calcd for $C_{30}H_{22}N_8O$ (%): C, 70.58; H, 4.34; N, 21.95. Found: C, 70.60; H, 4.32; N, 21.94%.

7-Imino-10-methyl-2,8,13-triphenyl-12,13-dihydropyrimido[4,5-*e*]pyrimido[1',2':2,3][1,2,4]triazolo-[1,5-*a*][1,4]diazepin-4(7*H*)-one (13). Compound **12** (0.510 g, 1 mmol) in sodium ethoxide (10 mL) was heated under reflux for 6 h. The reaction mixture was left to cool and poured onto ice and dil. HCl. The solid obtained was filtered off and recrystallized from EtOH to give compound **13** as pale brown crystals (0.306 g, 60%): mp 192-194 ºC; IR (ν cm^{-1}) 3390-3250 (2NH), 3025 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 1678 (C=O), 1600 (C=N), 1556 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 5.85 (s, 1H,

$CH_{methine}$), 7.40 (s, 2H, 2NH exchangeable with D_2O), 7.52-7.84 (m, 15 H, Ar-H), 8.20 (s, 1H, H-3 $_{pyrimidinone}$); ^{13}C NMR (75 MHz) δ 24.4 (CH_3), 88.2 (-**C**HPh), 120.2, 121.9, 122.7, 123.5, 124.3, 125.6, 126.4, 126.8, 127.2, 127.4, 127.8, 128, 128.4, 128.8, 129.2, 130.6, 132.7, 134.5, 136.6, 156.8 (C=O); Anal. Calcd for $C_{30}H_{22}N_8O$ (%): C, 70.58; H, 4.34; N, 21.95. Found: C, 70.58; H, 4.34; N, 21.95%.

6-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-2-{[(7-oxo-5-phenyl-1,7-dihydro[1,2,4]triazolo[1,5-*a*]-pyrimidin-2-yl)(phenyl)methyl]amino}pyridine-3-carbonitrile (15). A mixture of compound **6** (0.336 g, 1 mmol) and 2-amino-6-(4-hydroxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (**14**) (0.317 g, 1 mmol) in DMF (5 mL) and catalytic amount of piperidine was heated under reflux for 4 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **15** as pale brown crystals (0.401 g, 65%): mp 203-205 ºC; IR (ν cm^{-1}) 3400, 3377, 3200 (2NH, OH), 3050 ($CH_{arom.}$), 2929 ($CH_{aliph.}$), 2205 (C≡N), 1670 (C=O), 1608 (C=N), 1576 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ 3.83 (s,3H, OCH_3), 5.80 (s, 1H, $CH_{methine}$), 6.79 (s, 1H, NH exchangeable with D_2O), 6.88 (s, 1H, NH exchangeable with D_2O), 6.84-6.87 (m, 5 H, Ar-H), 7.07-7.13 (m, 5 H, Ar-H), 7.62-7.64 (dd, 4 H, Ar-H), 7.98-8.01 (dd, 4 H, Ar-H), 7.61 (s, 1H, H-$5_{pyridine}$), 7.97 (s, 1H, H-$6_{pyrimidinone}$), 9.90 (s, 1H, OH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 56 (O**C**H_3), 89.3 (-**C**HPh), 114.8 (C≡N), 120, 120.4, 121.6, 121.8, 122.4, 124.2, 126.8, 127, 127.2, 127.8, 128, 128.6, 128.8, 129.8, 132.4, 134, 135.2, 135.8, 136.3, 138.2, 140.2, 141, 141.6, 142.4, 146.8, 168.6 (C=O); MS *m/z* (%): $[M]^{\cdot+}$ 617 (0.01), [M+1] 618 (0.01), 317 (100), 302 (8.2), 198 (7.8), 129 (2.5), 91 (1.4), 77 (4), 57 (3.2); Anal. Calcd for $C_{37}H_{27}N_7O_3$ (%): C, 71.95; H, 4.41; N, 15.87. Found: C, 71.98; H, 4.40; N, 15.88%.

7-Imino-2,13-Diphenyl-10-(4-hydroxyphenyl)-8-(4-methoxyphenyl)-12,13-dihydropyrido[2,3-*e*]-pyrimido[1',2':2,3][1,2,4]triazolo[1,5-*a*][1,4]diazepin-4(7*H*)-one (16). Compound **15** (0.617 g, 1 mmol) in sodium ethoxide (10 mL) was heated under reflux for 6 h. The reaction mixture was left to cool and poured onto ice and dil. HCl. The solid obtained was filtered off and recrystallized from EtOH to give compound **16** as pale brown crystals (0.376 g, 61%): mp 195-197 ºC; IR (ν cm^{-1}) 3390-3250 (2NH, OH), 3025 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 1678 (C=O), 1600 (C=N), 1556 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, OCH_3), 5.82 (s, 1H, $CH_{methine}$), 7.13 (s, 2H, 2NH exchangeable with D_2O), 6.86-6.89 (m, 5 H, Ar-H), 7.08-7.16 (m, 5 H, Ar-H), 7.64-7.66 (dd, 4 H, Ar-H), 7.99-8.02 (dd, 4 H, Ar-H), 7.58 (s, 1H, H-9 $_{pyridine}$), 7.85 (s, 1H, H-$3_{pyrimidinone}$), 10.10 (s, 1H, OH exchangeable with D_2O); ^{13}C NMR (75 MHz) δ 58.8 (O**C**H_3), 90.6 (-**C**HPh), 120.4, 120.8, 121.2, 122.8, 123.8, 124, 125.4, 126.8, 127.4, 128.2, 128.4, 128.8, 129.6, 130.8, 131.2, 133.2, 135.2, 135.7, 136.8, 137, 140.4, 141.7, 141.9, 142.4, 146.8, 148.2, 168.6 (C=O); Anal. Calcd for $C_{37}H_{27}N_7O_3$ (%): C, 71.95; H, 4.41; N, 15.87. Found: C, 71.95; H, 4.41; N, 15.87%.

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