Synthesis, characterization and antimicrobial evaluation of the novel pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines and thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines

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Abstract

Starting from ethyl 1,2-diamino-5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate, a novel series of polynuclear pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines and thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines have been synthesized. Structures of the newly synthesized products have been deduced on the basis of elemental analysis and spectral data. The synthesized compounds were screened for their antimicrobial activity.

Keywords: 1,2-Diaminopyridone, pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines, thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines, cyclocondensation

Introduction

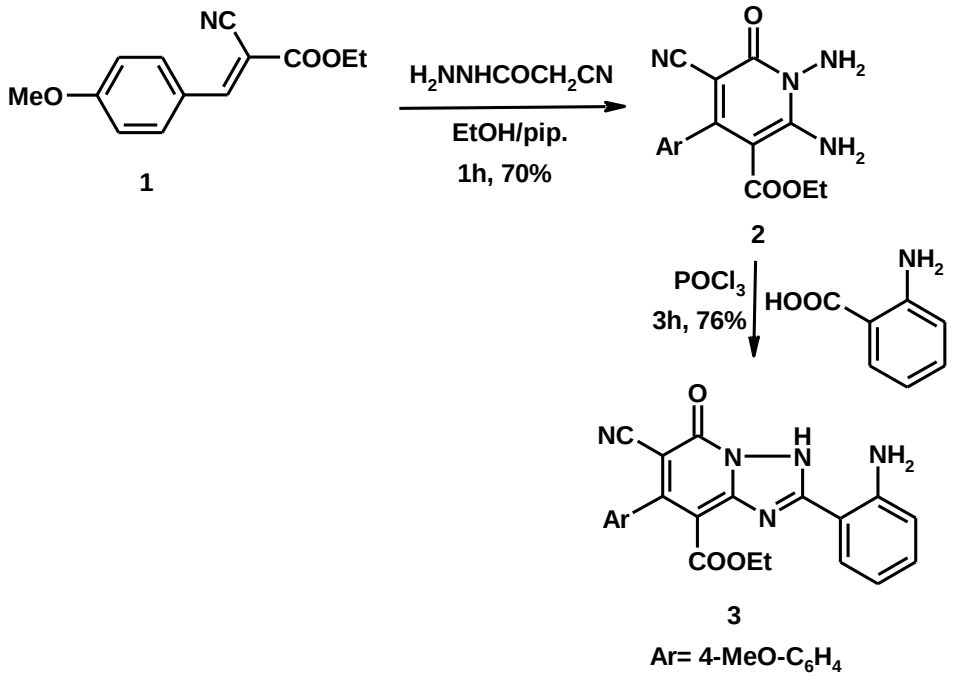
o-Diamines are very active substrates for building of various heterocyclic systems.[1-7] 4-Aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles have been used for the synthesis of biologically active nitrogen bridgehead triazolo[1,5-*a*]pyridines,[8-10] pyrido[1,2-*b*][1,2,4]triazines,[11-13] and pyrido[1,2-*b*][1,2,4]triazepines.[14,15] The present work aimed to utilize the diaminopyridone derivative **2** as a precursor to synthesis a novel series of polyheterocyclic systems namely pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines and thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines to evaluate their antimicrobial activity.

Results and Discussion

The starting compound ethyl 1,2-diamino-5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2**) was prepared by refluxing an alcoholic solution of ethyl 3-

cyano-2-(4-methoxyphenyl)prop-2-enoate (**1**) with cyanoacetohydrazide in absolute ethanol containing few drops of piperidine as a catalyst (Scheme 1).[16] The IR spectrum of compound **2** showed characteristic absorption bands at 3216, 3089, 3079 ($2NH_2$), 2255 (C≡N), 1692 ($C=O_{ester}$) and 1672 cm^{-1} ($C=O_{pyridone}$). Its mass spectrum revealed the molecular ion peak at m/z 328 which agree well with the molecular weight (328.33) as supports the identity of the structure.

Treating compound **2** with anthranilic acid in phosphorus oxychloride gave ethyl 2-(2-aminophenyl)-6-cyano-7-(4-methoxyphenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate (**3**) (Scheme 1).[17] The IR spectrum of compound **3** exhibited characteristic absorption bands at 3417, 3341, 3241 (NH_2, NH), 2189 (C≡N), 1678 ($C=O_{ester}$), 1652 ($C=O_{pyridone}$) and 1609 cm^{-1} (C=N). Also, its ^{1}H NMR spectrum showed exchangeable signals at δ 5.60 and 8.85 ppm assigned to the NH_2 and NH protons, respectively. The mass spectrum of compound **3** showed the molecular ion peak at m/z 429 which is coincident with the molecular weight (429.44) as supports the identity of the structure.

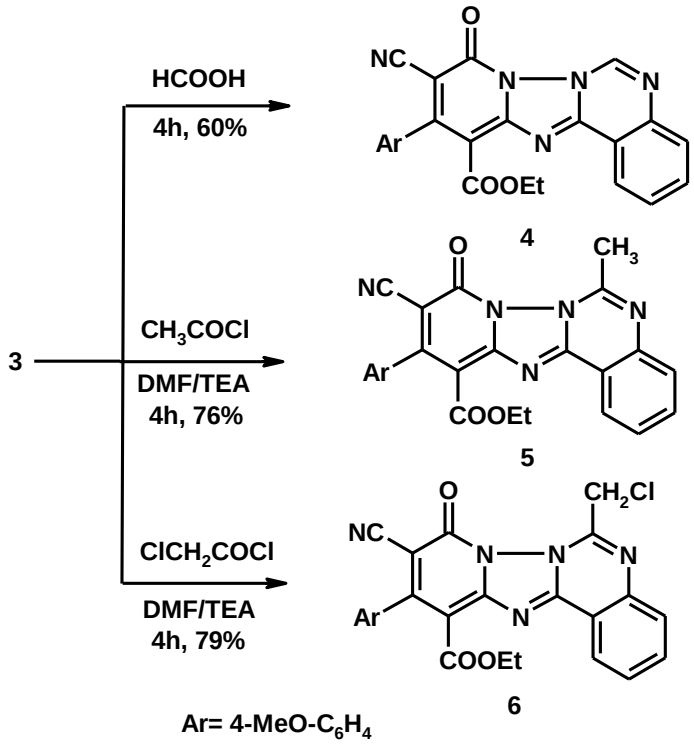


Scheme 1. Synthesis of diaminopyridone **2** and triazolopyridone **3**.

Compound **3** was used as a precursor for the synthesis of novel pyrido[1',2':2,3] [1,2,4]triazolo[1,5-*c*]quinazoline derivatives *via* the reaction with some electrophilic reagents. Thus, heterocyclization of compound **3** with formic acid afforded ethyl 3-cyano-2-(4-methoxyphenyl)-4-oxo-4,7-dihydro-pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazoline-1-carboxylate **(4)** (Scheme 2). The ^{1}H NMR spectrum of compound **4** showed two characteristic singlet signals at δ 3.86 and 8.63 ppm assigned to the OCH_3 and H-7, respectively. The mass

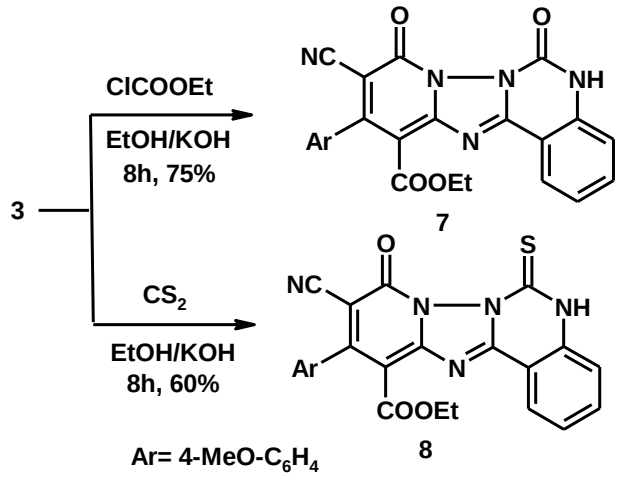
spectrum of compound **4** revealed the molecular ion peak at m/z 439 corresponding to the molecular formula $C_{24}H_{17}N_5O_4$, which agree well with the molecular weight (439.43) and supports the identity of the structure.

Also, condensation of compound **3** with acetyl chloride and chloroacetyl chloride in boiling DMF containing few drops of triethylamine (TEA) gave pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*] quinazoline derivatives **5** and **6**, respectively (Scheme 2). The ^{1}H NMR spectra of compounds **5** and **6** showed characteristic signals at δ 2.21 and 2.73 ppm assigned to the CH_3 and CH_2Cl protons, respectively. Also, the ^{13}C NMR spectrum of compound **5** showed characteristic signal attributed to $CH_{3\ pyrimidine}$ at δ 20.6 ppm. Further, the mass spectra of compounds **5** and **6** revealed the molecular ion peaks at m/z 453 and 487 which agree well with the molecular weights for compounds **5** and **6**, respectively.



Scheme 2. Synthesis of pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines **4**-**6**.

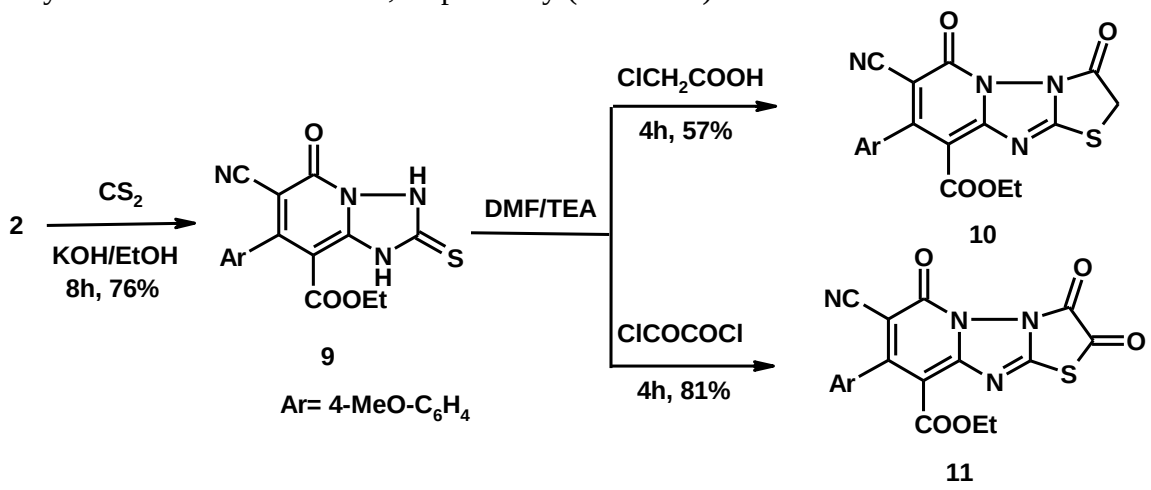
In the same manner, cyclocondensation of the starting material **3** with ethyl chloroformate and CS_2 in ethanolic potassium hydroxide solution afforded pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*] quinazolines **7** and **8**, respectively (Scheme 3). The mass spectra of compounds **7** and **8** showed the molecular ion peaks at m/z 455 and 471 corresponding to the molecular formulas $C_{24}H_{17}N_5O_5$ and $C_{24}H_{17}N_5O_4S$, respectively.



Scheme 3. Synthesis of pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazolines **7** and **8.**

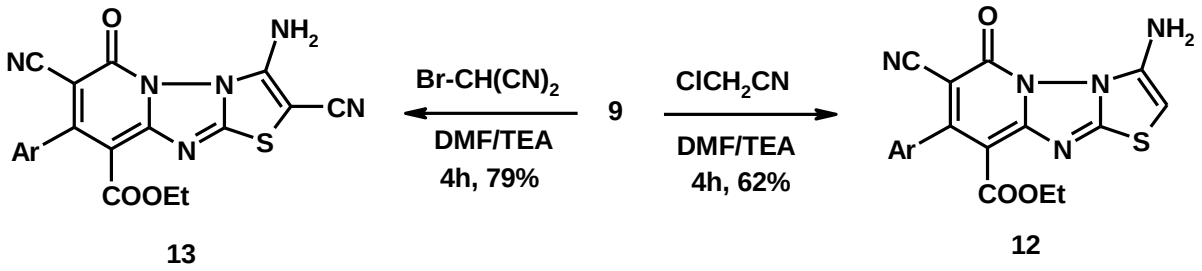
Next, the diaminopyridone derivative **2** was used as a starting material for the synthesis of a novel polyfused systems namely thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines. Thus, condensation of compound **2** with CS_2 in ethanolic KOH solution under reflux yielded ethyl 6-cyano-7-(4-methoxyphenyl)-5-oxo-2-thioxo-1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate (**9**) (Scheme 4).[18]

Compound **9** was allowed to react with some bifunctional electrophiles to produce the corresponding thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines **10**-**13**. Thus, heterocyclization of compound **9** with chloroacetic acid and oxalyl chloride in boiling DMF containing few drops of triethylamine produced the novel ethyl thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate derivatives **10** and **11**, respectively (Scheme 4).[19]



Scheme 4. Synthesis of thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines **10** and **11**.

Treatment of compound **9** with chloroacetonitrile and bromomalononitrile in boiling DMF containing few drops of triethylamine produced ethyl 3-amino-7-cyano-8-(4-methoxyphenyl)-6-oxo-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate (**12**) and ethyl 3-amino-2,7-dicyano-8-(4-methoxyphenyl)-6-oxo-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*] pyridine-9-carboxylate (**13**), respectively (Scheme 5).[20] The ^{1}H NMR spectrum of compound **12** showed a characteristic singlet at δ 6.18 ppm attributed to H-2, in addition to an exchangeable signal at δ 8.37 ppm assigned to the NH_2 protons, while the ^{1}H NMR spectrum of compound **13** showed an exchangeable signal at δ 8.41 ppm attributed to the NH_2 protons.



Scheme 5. Synthesis of thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines **12** and **13**.

Antimicrobial activity

The standardized disc agar diffusion method[21] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* and *Bacillus subtilis* as Gram-positive bacteria, *Salmonella typhimurium* and *Escherichia coli* as Gram-negative bacteria and *Candida albicans* as fungus strain. The compounds were dissolved in DMSO which has no inhibition activity to get concentration of 100 µg mL^{-1}. The test was performed on medium potato dextrose agars (PDA) which contain infusion of 200 g potatoes, 6 g dextrose and 15 g agar.[22] Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 µL) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface. After incubation for 36 h at 27 °C in the case of bacteria and for 48 h at 24 °C in the case of fungi, inhibition of the organisms was measured and used to calculate mean of inhibition zones.

The diaminopyridone derivative **2** showed lower activity towards all types of microorganisms while the synthesized polyfused systems exhibited lower to mild antimicrobial activity. From the results depicted in Table 1, we can conclude that:

1. Pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazoline derivatives **4**-**8** showed lower activity towards most of the microorganisms except compounds **7** and **8** showed moderate activity toward *Bacillus subtilis* as Gram-positive bacteria, also compound **8** showed moderate activity towards *Candida albicans* as fungus strain.
2. Thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines derivatives **10**-**13** showed moderate activity toward *Bacillus subtilis* as Gram-positive bacteria, *Salmonella typhimurium* as Gram-negative

bacteria and *Candida albicans* as fungus strain. Thus, the synthesized compounds may be considered promising for the development of new antimicrobial agents.

Conclusions

In the present work, a novel series of polynuclear pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*] quinazolines **4**-**8** and thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridines **10**-**13** were efficiently synthesized *via* the key intermediate ethyl 1,2-diamino-5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2**).

Table 1. The antimicrobial activity of the synthesized compounds **2**-**13**

	Mean* of zone diameter, nearest whole mm.									
	Gram - positive bacteria				Gram - negative bacteria				Fungi	
Organisms	*Staphylococcus aureus* (ATCC 25923))		*Bacillus subtilis* (ATCC 6635)		*Salmonella typhimurium* (ATCC 14028)		*Escherichia coli* (ATCC 25922)		*Candida albicans* (ATCC 10231)	
	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml
2	7 L	6 L	6L	4 L	-	-	8 L	6 L	7 L	6 L
3	8 L	6 L	8 L	7 L	8 L	5 L	10 L	7 L	6 L	4 L
4	-	-	9 L	6 L	-	-	12 L	8 L	7 L	4 L
5	8 L	7 L	9 L	7 L	9 L	7 L	11 L	8 L	7 L	5 L
6	8 L	7 L	10 L	6 L	9 L	7 L	12 L	8 L	7 L	4 L
7	-	-	14 I	10 I	-	-	-	-	7 L	4 L
8	-	-	19 I	15 I	10 L	7 L	11 L	8 L	13 I	11 I
9	10 L	8 L	-	-	8 L	7 L	10 L	9 L	15 I	10 I
10	9 L	7 L	16 I	14 I	14 I	12 I	10 L	9 L	14 I	9 L
11	9 L	7 L	17 I	14 I	13 I	12 I	7 L	7 L	18 I	14 I
12	8 L	8 L	12 I	9 L	14 I	10 I	6 L	6 L	16 I	13 I
13	9 L	7 L	12 I	10 I	16 I	12 I	7 L	7 L	12 I	8 L
Control #	35	26	35	25	36	28	38	27	35	28

* = Calculate from 3 values. - = No effect. L: Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of control. I: Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of control. H: High activity = Mean of zone diameter > 2/3 of mean zone diameter of control. #: Chloramphenicol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria and cycloheximide in the case of fungi.

Experimental Section

General. Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR (300MHz) spectra were measured on Mercury-300BB, while ^{13}C NMR (125 MHz) spectra were measured on Jeol-Eca500 MHz, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography mass spectrometry instrument (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

Ethyl 1,2-diamino-5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (2). A mixture of ethyl 3-cyano-2-(4-methoxyphenyl)prop-2-enoate (**1**) (2.31 g, 10 mmol) and cyanoacetohydrazide, (0.99 g, 10 mmol), in absolute ethanol (40 mL) containing two drops of piperidine, was heated under reflux for 1h. The yellow crystals obtained during heating were filtered off and crystallized from DMF/EtOH to give compound **2** as white crystals, yield 2.33 g (70%), mp 215-216 ºC. IR (KBr, cm^{-1}): 3216, 3089, 3079 (2 NH_2), 3012 ($CH_{arom.}$), 2965, 2947, 2919, 2836 ($CH_{aliph.}$), 2255 (C≡N), 1692 ($C=O_{ester}$), 1672 ($C=O_{pyridone}$), 1607 (C=C). ^1H NMR (DMSO-d_6, δ): 1.22 (t, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.15 (q, 2H, CH_2), 5.62 (bs, 2H, N-NH_2 exchangeable with D_2O), 6.97 (d, 2H, Ar-H), 7.62 (d, 2H, Ar-H), 8.01 (bs, 1H, C-NH_2 exchangeable with D_2O), 8.81 (bs, 1H, C-NH_2 exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 12.9 (CH_3), 55.8 (OCH_3), 62.0 (CH_2), 87.2 (C-5), 114.8, 114.9, 116.6, 126.9, 129.4, 148.2, 159.1, 161.4, 161.6, 165.0. *m/z* (*I* %): 328 (45), 312 (43), 298 (68), 284 (47), 212 (68), 196 (66), 157 (57), 130 (54), 107 (46), 77 (91), 69 (100). Analysis Calcd for $C_{16}H_{16}N_4O_4$ (328.33); C, 58.53; H, 4.91; N, 17.06%. Found: C, 58.36; H, 4.72; N, 16.84%.

Ethyl 2-[(2-aminophenyl)]-6-cyano-7-[(4-methoxyphenyl)]-5-oxo-3,5-dihydro-[1,2,4] triazolo[1,5-*a*]pyridine-8-carboxylate (3). A mixture of compound **2** (0.66 g, 2 mmol) and anthranilic acid (0.27 g, 2 mmol) in $POCl_3$ (10 mL) was heated under reflux on a water bath for 3h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF/MeOH to give compound **3** as yellow crystals, yield 0.65 g (76 %), mp 186-187 °C. IR (KBr, cm^{-1}): 3417, 3341, 3241 (NH_2, NH), 3005 ($CH_{arom.}$), 2950, 2932, 2837 ($CH_{aliph.}$), 2189 (C≡N), 1678 ($C=O_{ester}$), 1652 ($C=O_{pyridone}$), 1609 (C=N), 1585 (C=C). ^1H NMR (DMSO-d_6): 1.23 (t, 3H, CH_3), 3.72 (q, 2H, CH_2), 3.85 (s, 3H, OCH_3), 5.60 (bs, 2H, NH_2 exchangeable with D_2O), 6.81-6.87 (m, 2H, Ar-H), 7.02-7.36 (m, 4H, Ar-H), 7.50-7.64 (m, 2H, Ar-H), 8.85 (bs, 1H, NH exchangeable with D_2O). *m/z* (*I* %): 429 (11), 415 (22), 403 (28), 385 (14), 372 (69), 356 (32), 339 (85), 310 (98), 252 (18), 119 (24), 108 (23), 78 (7), 64 (100). Analysis Calcd for $C_{23}H_{19}N_5O_4$ (429.44); C, 64.33; H, 4.46; N, 16.31%. Found: C, 64.08; H, 4.34; N, 16.17%.

Ethyl 3-cyano-2-(4-methoxyphenyl)-4-oxo-4,7-dihydro-pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazoline-1-carboxylate (4). A mixture of compound **3** (0.86 g, 2 mmol) and formic acid (10 mL) was heated under reflux for 4h. After cooling, the reaction mixture was poured onto

ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from EtOH to give compound **4** as yellow crystals, yield 0.53 g (60%), mp 201-202 °C. IR (KBr, cm^{-1}): 3020 ($CH_{arom.}$), 2935, 2922, 2851 ($CH_{aliph.}$), 2219 (C≡N), 1654 ($C=O_{ester}$ and $C=O_{pyridone}$), 1607 (C=N), 1586 (C=C). ^{1}H NMR (DMSO-d_6): 1.17 (t, 3H, CH_3), 3.71 (q, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.83 (d, 2H, Ar-H, *J* 8.7 Hz), 7.05 (d, 2H, Ar-H, *J* 8.7 Hz), 7.51 (t, 1H, Ar-H, *J* 8.7 Hz), 7.61 (d, 1H, Ar-H, *J* 8.7 Hz), 7.67-7.88 (m, 2H, Ar-H), 8.63 (s, 1H, H-7 as CH=N). *m/z* (*I* %): 439 (2), 411 (2), 366 (3), 336 (6), 306 (4), 280 (3), 262 (2), 107 (13), 93 (11), 77 (5), 57 (100). Analysis Calcd for $C_{24}H_{17}N_5O_4$ (439.43); C, 65.60; H, 3.90; N, 15.94%. Found: C, 65.42; H, 3.82; N, 15.71%.

Ethyl 3-cyano-2-(4-methoxyphenyl)-7-methyl-4-oxo-4*H*-pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazoline-1-carboxylate (5). A mixture of compound **3** (0.86 g, 2 mmol) and acetyl chloride (0.14 mL, 2 mmol), in DMF containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF to give compound **5** as yellow crystals, yield 0.69 g (76%), mp 225-226 °C. IR (KBr, cm^{-1}): 3035 ($CH_{arom.}$), 2940, 2924, 2852 ($CH_{aliph.}$), 2216 (C≡N), 1685 ($C=O_{ester}$ and $C=O_{pyridone}$), 1607 (C=N), 1597 (C=C). ^{1}H NMR (DMSO-d_6): 1.16 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.71 (q, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.82 (d, 2H, Ar-H, *J* 8.7 Hz), 7.09 (d, 2H, Ar-H, *J* 8.7 Hz), 7.43-7.81 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 12.7 (CH_3), 20.6 ($CH_{3\ pyrimidine}$), 56.6 (OCH_3), 61.8 (CH_2), 110.4, 114.9, 116.3, 116.5, 118.1, 128.0, 128.6, 130.5, 131.8, 131.9, 134.5, 147.1, 147.2, 151.6, 158.2, 161.3, 161.6, 166.9, 167.1. *m/z* (*I* %): 453 (14), 438 (7), 425 (21), 399 (17), 384 (34), 314 (18), 289 (26), 247 (43), 155 (54), 98 (49), 81 (73), 57 (100). Analysis Calcd for $C_{25}H_{19}N_5O_4$ (453.46); C, 66.22; H, 4.22; N, 15.44%. Found: C, 66.03; H, 3.94; N, 15.12%.

Ethyl 7-chloromethyl-3-cyano-2-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1',2':2,3][1,2,4] triazolo[1,5-*c*]quinazoline-1-carboxylate (6). A mixture of compound **3** (0.86 g, 2 mmol) and chloroacetyl chloride (0.16 mL, 2 mmol), in DMF containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF/H_2O to give compound **6** as yellow crystals, yield 0.77 g (79%), mp 126-127 °C. IR (KBr, cm^{-1}): 3003 ($CH_{arom.}$), 2931, 2831 ($CH_{aliph.}$), 2222 (C≡N), 1683 ($C=O_{ester}$), 1651 ($C=O_{pyridone}$), 1608 (C=N), 1576 (C=C). ^{1}H NMR (DMSO-d_6): 1.22 (t, 3H, CH_3), 2.73 (s, 2H, CH_2Cl), 3.70 (q, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.82-7.85 (m, 8H, Ar-H). *m/z* (*I* %): 489 (M+2; 4), 487 (M^+,12), 472 (5), 458 (34), 363 (9), 252 (33), 227 (24), 149 (39), 135 (18), 92 (26), 57 (100). Analysis Calcd for $C_{25}H_{18}ClN_5O_4$ (487.91); C, 61.54; H, 3.72; N, 14.35%. Found: C, 61.19; H, 3.54; N, 14.17%.

Ethyl 3-cyano-2-(4-methoxyphenyl)-4,7-dioxo-4,7-dihydro-8*H*-pyrido[1',2':2,3][1,2,4] triazolo[1,5-*c*]quinazoline-1-carboxylate (7). A mixture of compound **3** (0.86 g, 2 mmol) and ethyl chloroformate (0.22 g, 0.2 mL, 2 mmol) in ethanolic potassium hydroxide (2%, 30 mL) was heated under reflux for 8h. After cooling, the reaction mixture was poured onto ice/water and neutralized with conc. HCl. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF/EtOH to give compound **7** as yellow crystals, yield 0.68 g

(75%), mp 300-301 °C. IR (KBr, cm^{-1}): 3423 (NH), 2933, 2921, 2850 ($CH_{aliph.}$), 2213 (C≡N), 1680 ($C=O_{ester}$), 1651 ($C=O_{pyridone}$ and $C=O_{pyrimidinone}$), 1606 (C=N and C=C). ^{1}H NMR (DMSO-d_6): 1.15 (t, 3H, CH_3), 3.69 (q, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.84-7.65 (m, 8H, Ar-H). *m/z* (*I* %): 455 (3), 454 (8), 399 (2), 358 (8), 284 (3), 271 (13), 256 (16), 238 (18), 135 (88), 120 (87), 77 (19), 57 (100). Analysis Calcd for $C_{24}H_{17}N_5O_5$ (455.43); C, 63.30; H, 3.76; N, 15.38%. Found: C, 63.21; H, 3.58; N, 15.14%.

Ethyl 3-cyano-2-(4-methoxyphenyl)-4-oxo-7-thioxo-4,7-dihydro-8*H*-pyrido[1',2':2,3][1,2,4]triazolo[1,5-*c*]quinazoline-1-carboxylate (8). A mixture of compound **3** (0.86 g, 2 mmol) and carbon disulfide (0.12 mL, 2 mmol) in ethanolic potassium hydroxide solution (2%, 30 mL) was heated under reflux for 8h. After cooling, the reaction mixture was poured onto ice/water and neutralized with conc. HCl. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF/EtOH to give compound **8** as yellow crystals, yield 0.56 g (60%), mp 231-232 ºC. IR (KBr, cm^{-1}): 3420 (NH), 2938, 2925, 2845 ($CH_{aliph.}$), 2216 (C≡N), 1686 ($C=O_{ester}$), 1654 ($C=O_{pyridone}$), 1607 (C=N), 1576 (C=C), 1251 (C=S). ^{1}H NMR (DMSO-d_6): 1.24 (t, 3H, CH_3), 3.72 (q, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.85 (d, 2H, Ar-H, *J* 9.0 Hz), 7.12 (d, 2H, Ar-H, *J* 9.0 Hz), 7.40-7.94 (m, 4H, Ar-H), 8.20 (bs, 1H, NH exchangeable with D_2O). *m/z* (*I* %): 471 (76), 442 (9), 363 (33), 256 (35), 224 (16), 80 (39), 64 (100). Analysis Calcd for $C_{24}H_{17}N_5O_4S$ (471.50); C, 61.14; H, 3.63; N, 14.85; S, 6.80%. Found: C, 61.11; H, 3.58; N, 14.57; S, 6.61%.

Ethyl 6-cyano-7-(4-methoxyphenyl)-5-oxo-2-thioxo-1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate (9). A mixture of compound **3** (0.67 g, 2 mmol) and carbon disulfide (0.12 mL, 2 mmol) in ethanolic potassium hydroxide solution (2%, 30 mL) was heated under reflux for 8h. After cooling, the reaction mixture was poured onto ice/water and neutralized with conc. HCl. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF/EtOH to give compound **9** as yellow crystals, yield 0.56 g (76%), mp 174-175 °C. IR (KBr, cm^{-1}): 3279 (2NH), 3110 ($CH_{arom.}$), 2910, 2854 ($CH_{aliph.}$), 2205 (C≡N), 1683 ($C=O_{ester}$ and $C=O_{pyridone}$), 1588 (C=C), ^{1}H NMR (DMSO-d_6): 1.17 (t, 3H, CH_3, *J* 7.2 Hz), 3.04 (q, 2H, CH_2, *J* 7.2 Hz), 3.82 (s, 3H, OCH_3), 7.04 (d, 2H, Ar-H, *J* 9.0 Hz), 7.80 (d, 2H, Ar-H, *J* 8.7 Hz), 8.63 (bs, 2H, 2NH exchangeable with D_2O). Analysis Calcd for $C_{17}H_{14}N_4O_4S$ (370.39); C, 55.13; H, 3.81; N, 15.13; S, 8.66%. Found: C, 55.21; H, 3.65; N, 14.92; S, 8.38%.

Ethyl 7-cyano-8-(4-methoxyphenyl)-3,6-dioxo-2,3-dihydro-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate (10). A mixture of compound **9** (0.74 g, 2 mmol) and chloroacetic acid (0.17 g, 2 mmol), in DMF (10 mL) containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from methanol to give compound **10** as yellow crystals, yield 0.47 g (57%), mp 298-299 ºC. IR (KBr, cm^{-1}): 3033 ($CH_{arom.}$), 2924, 2890 ($CH_{aliph.}$), 2224 (C≡N), 1706 ($C=O_{ester}$), 1657 ($C=O_{pyridone}$), 1603 (C=N and C=C). ^{1}H NMR (DMSO-d_6): 1.16 (t, 3H, CH_3), 3.09 (q, 2H, CH_2), 3.65 (s, 2H, $CH_2C=O$), 3.87 (s, 3H, OCH_3), 7.56 (d, 2H, Ar-H), 7.84 (d, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 13.1 (CH_3), 36.8 ($CH_{2\ thiazole}$), 55.5 (OCH_3), 62.4 (CH_2), 103.2, 114.6, 114.9, 116.8, 128.9, 130.8,

148.0, 149.2, 158.0, 161.4, 162.6, 165.5, 167.2. Analysis Calcd for $C_{19}H_{14}N_4O_5S$ (410.41); C, 55.61; H, 3.44; N, 13.65; S, 7.81%. Found: C, 55.48; H, 3.30; N, 13.52; S, 7.72%.

Ethyl 7-cyano-8-(4-methoxyphenyl)-2,3,6-trioxo-2,3-dihydro-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate (11). A mixture of compound **9** (0.74 g, 2 mmol) and oxalyl chloride (0.18 mL, 2 mmol), in DMF (10 mL) containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from DMF to give compound **11** as yellow crystals, yield 0.69 g (81%), mp 274-275 ºC. IR (KBr, cm^{-1}): 3080 ($CH_{arom.}$), 2924, 2848 ($CH_{aliph.}$), 2223 (C≡N), 1739, 1660 (4C=O), 1580 (C=N) and 1543 (C=C). ^{1}H NMR (DMSO-d_6): 1.14 (t, 3H, CH_3), 3.03 (q, 2H, CH_2), 3.87 (s, 3H, OCH_3), 7.49 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H). Analysis Calcd for $C_{19}H_{12}N_4O_6S$ (424.39); C, 53.77; H, 2.85; N, 13.20; S, 7.56%. Found: C, 53.41; H, 2.56; N, 12.84; S, 7.32%.

Ethyl 3-amino-7-cyano-8-(4-methoxyphenyl)-6-oxo-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate (12). A mixture of compound **9** (0.74 g, 2 mmol) and chloroacetonitrile (0.12 mL, 2 mmol), in DMF (10 mL) containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from methanol to give compound **12** as yellow crystals, yield 0.51 g (62%), mp 257-258 ºC. IR (KBr, cm^{-1}): 3436, 3280 (NH_2), 3016 ($CH_{arom.}$), 2960, 2833 ($CH_{aliph.}$), 2224 (C≡N), 1718 ($C=O_{ester}$), 1670 ($C=O_{pyridone}$), 1596 (C=N), 1554 (C=C). ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, CH_3), 3.74 (q, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.18 (s, 1H, H-2), 7.09 (d, 2H, Ar-H, *J* 7.5 Hz), 7.46 (d, 2H, Ar-H, *J* 7.5 Hz), 8.37 (bs, 2H, NH_2 exchangeable with D_2O). Analysis Calcd for $C_{19}H_{15}N_5O_4S$ (409.43); C, 55.74; H, 3.69; N, 17.11; S, 7.83%. Found: C, 55.52; H, 3.72; N, 17.14; S, 7.59%.

Ethyl 3-amino-2,7-dicyano-8-(4-methoxyphenyl)-6-oxo-6*H*-[1,3]thiazolo[3',2':2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carboxylate (13). A mixture of compound **9** (0.74 g, 2 mmol) and bromomalononitrile (2 mmol), in DMF (10 mL) containing few drops of triethylamine, was heated under reflux for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered off, washed with water, air dried and crystallized from ethanol to give compound **13** as yellow crystals, yield 0.69 g (79%), mp 310-311 ºC. IR (KBr, cm^{-1}): 3438, 3332 (NH_2), 3104 ($CH_{arom.}$), 2925, 2850 ($CH_{aliph.}$), 2219 (2C≡N), 1695 ($C=O_{ester}$ and $C=O_{pyridone}$), 1619 (C=N), 1548 (C=C). ^{1}H NMR (DMSO-d_6): 1.26 (t, 3H, CH_3), 3.03 (q, 2H, CH_2), 3.97 (s, 3H, OCH_3), 7.55 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 8.41 (bs, 2H, NH_2 exchangeable with D_2O). Analysis Calcd for $C_{20}H_{14}N_6O_4S$ (434.44); C, 55.30; H, 3.25; N, 19.34; S, 7.38%. Found: C, 55.12; H, 3.01; N, 19.08; S, 7.24%.

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