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SYNTHESIS OF SOME NEW NITROGEN BRIDGE-HEAD PYRIDO[1,2,4]TRIAZEPINES

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Ring closure reactions of 1,6-diamino-4-(4-chlorophenyl)-2-oxopyridine-3,5-dicarbonitrile with various 1,3-dielectrophiles, namely, diethyl malonate, ethyl ethoxymethylenecyanoacetate, 2-cyano-3,3-bis(methylthio)acrylonitrile, dimethyl acetylenedicarboxylate, dehydroacetic acid, chromone-3-carbonitrile, and 3-formylchromone led to the formation of the target biheterocyclic 1,2,4-triazepines. The reactions with 3-phenylazo-2,4-pentadione, ethyl α-cyano-α-phenylazoacetate, and 3,1-benzoxazin-4-one derivative are also described.

Keywords: pyridotriazepines, pyridotriazines, triazolopyridines.

It has been shown that condensed triazepines exhibit important pharmacological activities [1–4]. Most of the reported condensed triazepines are from the types [1,2,5]-, [1,3,5]-, and [1,3,4]triazepines such as benzo[1,2,5]triazepines [5, 6], triazolo[1,2,5]triazepines [7], benzo[1,3,5]triazepines [8], and benzo-[1,3,4]triazepines [9]. In contrast, the biheterocyclic 1,2,4-triazepines are relativity rare. A few examples were seen in the literature such as thiazolo[1,2,4]triazepines [10, 11], oxadiazolo- and isoxazolo[1,2,4]triazepines [12], and pyrazolopyrimido[1,2,4]triazepines [13]. As a part of our program directed to the synthesis of new polynuclear bioactive heterocyclic systems [14-17], the present synthetic strategy is designed to utilize 1,6-diamino-4-(4-chlorophenyl)-2-oxopyridine-3,5-dicarbonitrile (**1**) as a suitable starting material for the synthesis of nitrogen bridge-head pyrido[1,2,4]triazepines of expected biological activity.

It is well known that compounds having vicinal amino groups are good precursors for building many condensed heterocycles [18, 19]. Compound **1** as an example of such compounds was used in the synthesis of triazolopyridines [20-22] and pyridotriazines [22, 23], but until now only a few examples of pyrido[1,2-*b*]-[1,2,4]triazepines are known [22, 24]. Therefore, we used compound **1** to synthesize some novel pyrido-[1,2-*b*][1,2,4]triazepines *via* ring closure reactions with some interesting 1,3-dielectrophiles. Thus, when 1,6-diamino pyridine derivative **1** was allowed to react with diethyl malonate in boiling DMF, 9-(4-chlorophenyl)-2,4,7-trioxo-1,3,5-trihydropyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (**2**) was obtained. The ^{1}H NMR spectrum of compound **2** showed a singlet signal at δ 3.35 ppm due to the CH_2 protons in addition to two exchangeable singlets at δ 5.67 and 8.52 ppm assigned to N–NH and C–NH protons, respectively. The treatment of compound **1** with ethyl ethoxymethylenecyanoacetate may afford two possible pyridotriazepine

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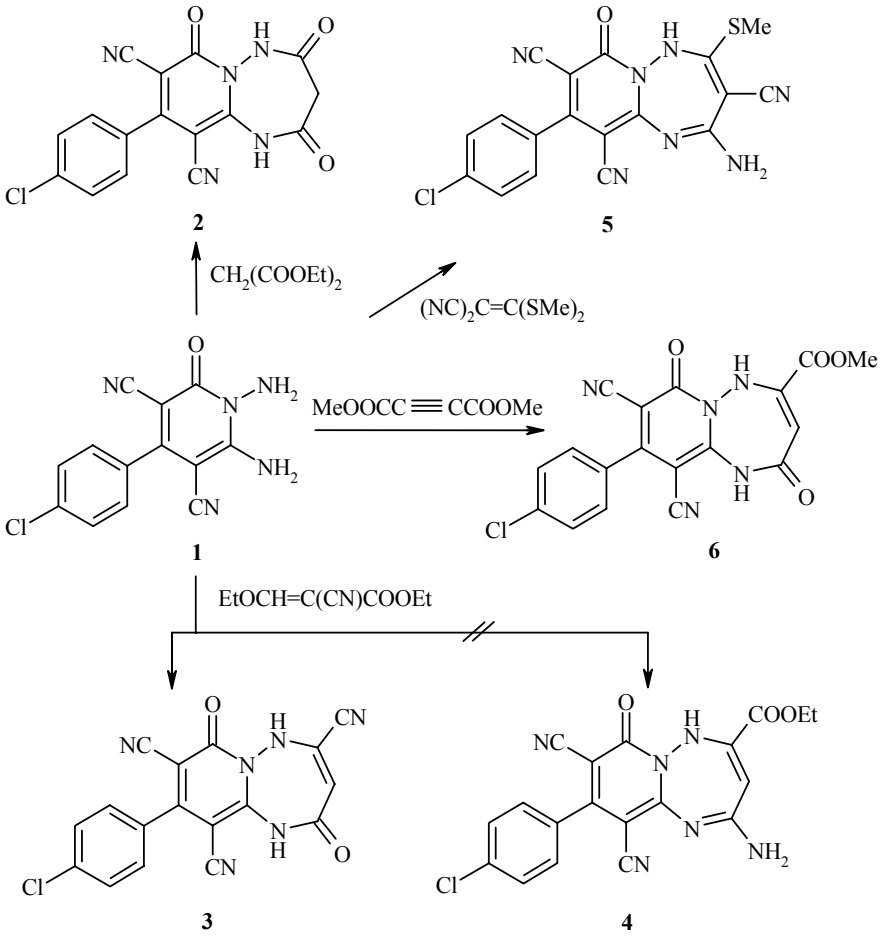
derivatives **3** and **4**. Compound **4** was ruled out due to the absence of triplet and quartet signals attributed to the ethoxy group in the ^{1}H NMR spectrum. Compound **3** showed a characteristic singlet signal at δ 7.79 ppm attributed to H-3 proton. The formation of compound **3** proceeds *via* nucleophilic replacement of the ethoxy group followed by cyclocondensation losing one ethanol molecule.

Ketene dithioacetals are very useful building blocks to incorporate two or three carbon units in the construction of a variety of heterocyclic compounds. Thus, the treatment of compound **1** with 2-cyano-3,3-bis-(methylthio)acrylonitrile afforded 2-amino-9-(4-chlorophenyl)-4-methylthio-7-oxo-5H-pyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile (**5**). The reaction proceeds through an addition–elimination mechanism, which starts with nucleophilic addition at the sp^2 sulfur-substituted carbon atom of ketene dithioacetal followed by elimination of the methanethiol molecule with a cascade addition to the nitrile function to produce the target product **5**.

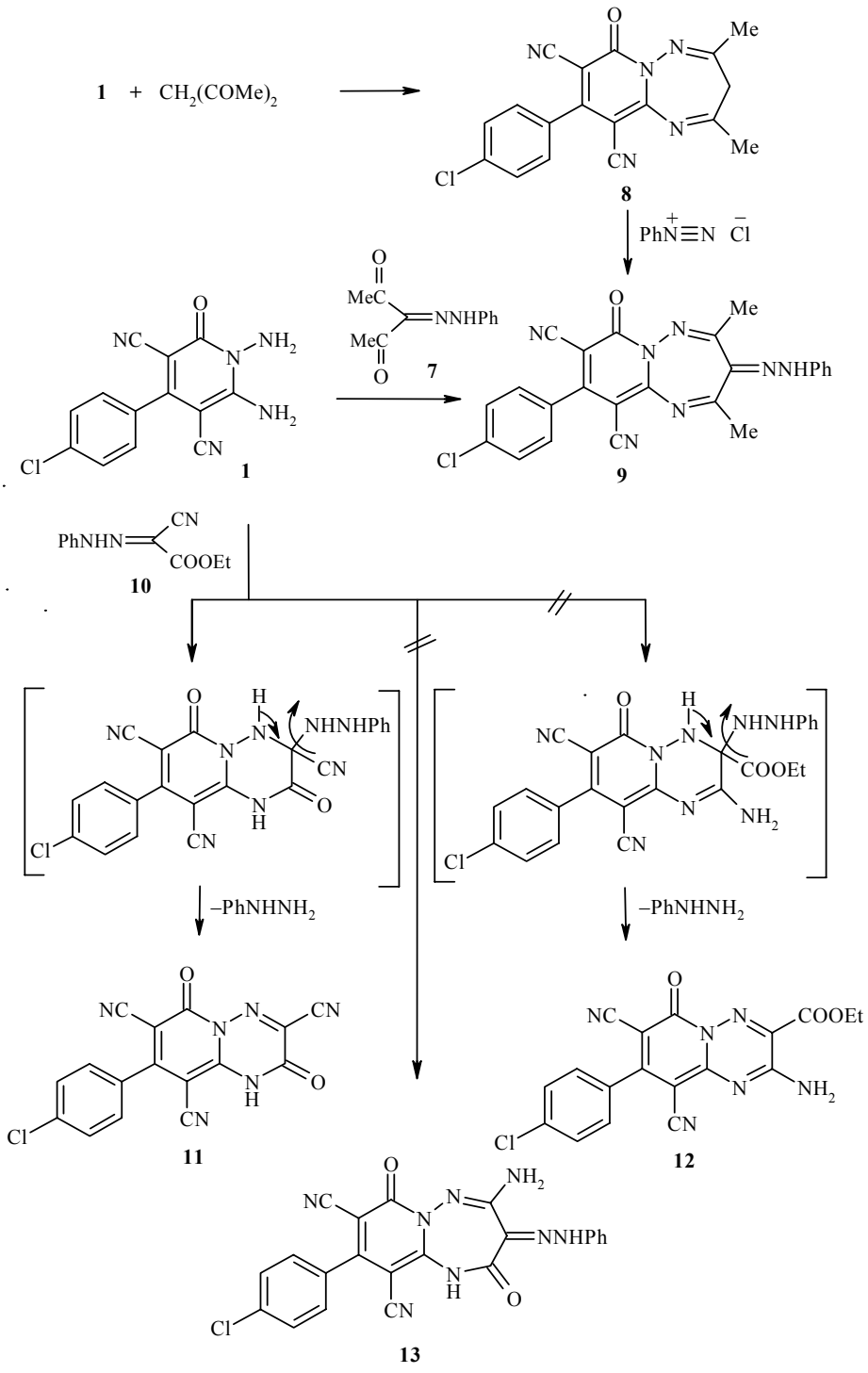
On the other hand, a new derivative of pyridotriazepine **6** was obtained from the reaction of the starting diamino compound **1** with dimethyl acetylenedicarboxylate. The IR spectrum of compound **6** showed absorption bands at 3412, 3344 (2NH), and 1710 cm^{-1} (C=O ester). Its ^{1}H NMR spectrum showed a characteristic singlet signals at δ 2.90 and 7.95 ppm assigned to CH_3 and H-3 protons, respectively, in addition to two exchangeable signals at δ 5.67 and 8.53 ppm corresponding to 2NH protons.

Scheme 1



Herein, the chemical reactivity of compound **1** was studied towards 3-phenylazo-2,4-pentanedione (**7**) and ethyl α-cyano-α-phenylazoacetate (**10**) [19]. Thus, the treatment of compound **1** with **7** afforded 9-(4-chlorophenyl)-2,4-dimethyl-7-oxo-3-phenylhydrazono-1H-pyrido[1,2-*b*][1,2,4]triazepine-8,10-tricarbonitrile (**9**).

Scheme 2

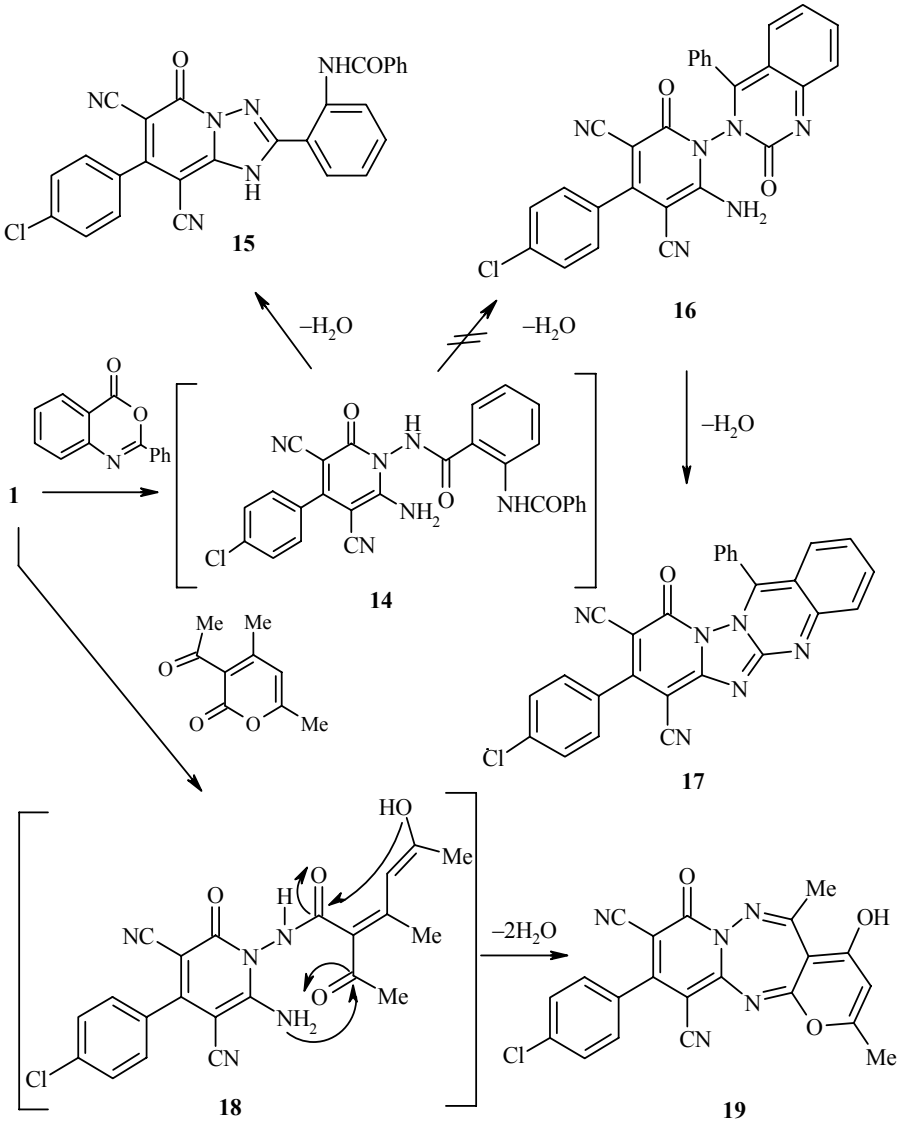


The latter compound **9** was also obtained authentically from the coupling of phenyldiazonium chloride with compound **8**, which was prepared from the condensation of the starting material **1** with acetyl acetone [24] in glacial acetic acid. The structure of compound **9** was deduced from elemental analysis and spectral data. Its ^{1}H NMR spectrum showed only one exchangeable signal at δ 8.52 ppm assigned to the NH proton, in addition to two singlet signals at δ 2.31 and 2.47 ppm attributed to 2- and 4-CH_3 protons.

On the other hand, ethyl α-cyano-α-phenylazoacetate showed a different behavior towards compound **1,** producing 8-(4-chlorophenyl)-2,6-dioxo-1H-pyrido[1,2-*b*][1,2,4]triazine-3,7,9-tricarbonitrile (**11**). The reaction may proceed through nucleophilic addition of the amino (N–NH_2) group to the highly activated carbon atom (N=C) followed by cyclization with losing one molecule of ethanol and subsequent elimination of one molecule of phenylhydrazine to produce compound **11**. The other possible products **12** and **13** were excluded on the basis of elemental analysis and spectral data. The ^{1}H NMR spectrum of the product did not show the ethoxy protons that appeared in **12** and the phenyl protons present in compound **13** (Scheme 2).

Moreover, the reaction of diamino compound **1** with some cyclic oxygenated compounds such as benzoxazinone and dehydroacetic acid was deduced. Thus, when compound **1** reacted with 2-phenyl-4H-3,1-benzoxazin-4-one [25] in dry pyridine, [1,2,4]triazolo[2,3-*a*]pyridinedicarbonitrile **15** was obtained through the formation of intermediate **14**, which on dehydration yielded compound **15** and not compounds **16** or **17**. The ^{1}H NMR spectrum of compound **15** revealed the presence of two deshielded protons at δ 12.18 and 8.56 ppm due to the two NH protons in addition to the aromatic protons, which were observed in the range of δ 7.22-8.09 ppm. On the other hand, the treatment of compound **1** with dehydroacetic acid in glacial acetic acid afforded pyrano[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazepine **19** *via* intermediate **18**. The structure of compound **19** was elucidated

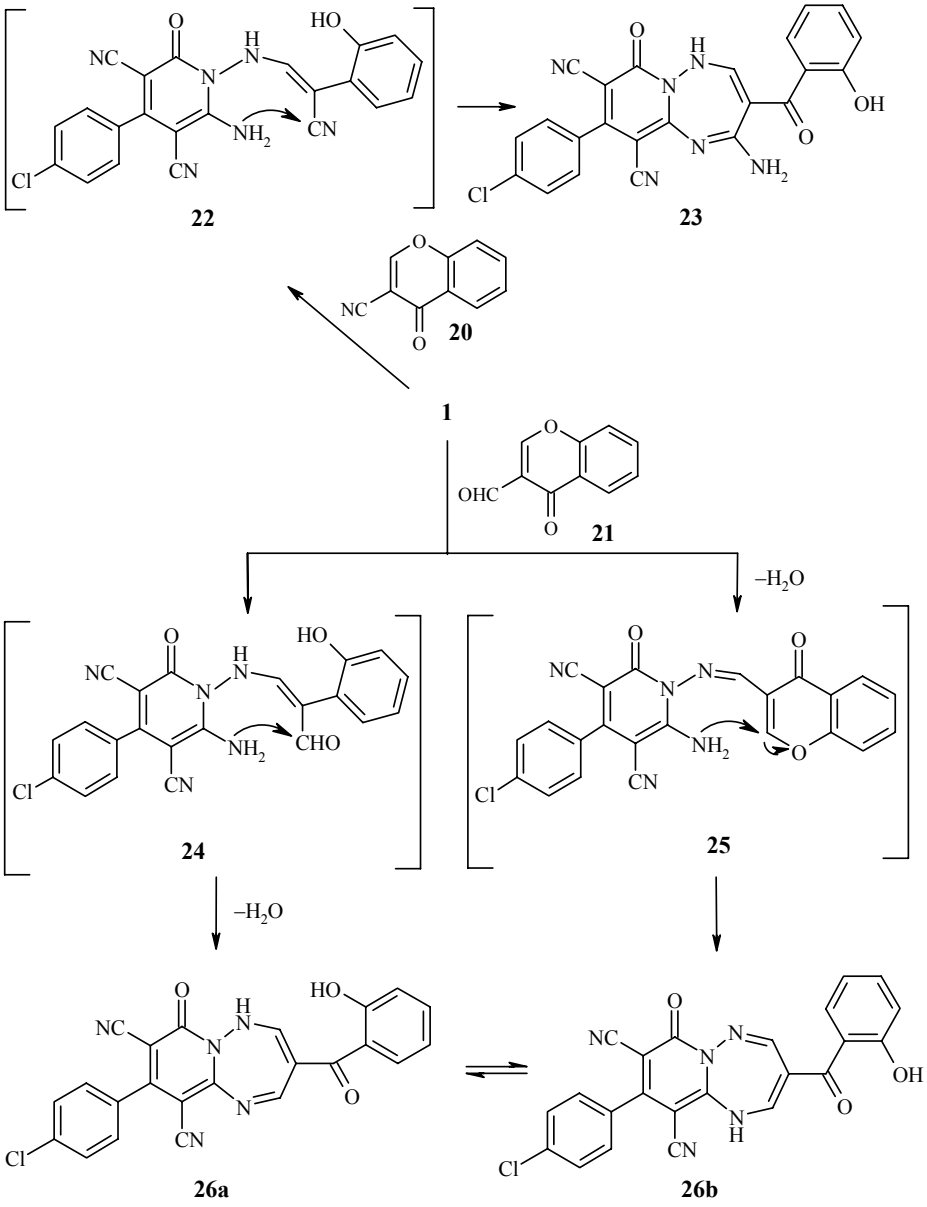
Scheme 3



from its elemental analysis and spectral data. The IR spectrum exhibited one absorption band at 1655 cm^{-1} corresponding to C=O of the pyridone system. The ^1H NMR spectrum showed two singlets at δ 2.56 and 3.34 ppm assigned to the two methyl groups in addition to a characteristic signal at δ 7.95 ppm attributed to the H-3 proton; the replaceable signal at δ 8.50 ppm was assigned to the OH proton (Scheme 3).

Also, the research was extended to study the effect of 1,6-diaminopyridone **1** towards very active substrates named chromone-3-carbonitrile (**20**) and chromone-3-carboxaldehyde (**21**) with the aim to prepare some novel 1,2,4-triazepine derivatives. Thus, the treatment of compound **1** with compounds **20** and **21** afforded pyrido[1,2-*b*][1,2,4]triazepines **23** and **26**, respectively. The latter two products gave a positive coloration with iron(III) chloride solution due to the presence of phenolic OH group. Formation of compound **23** proceeds *via* ring opening at C-2 of γ-pyrone to give compound **22,** then addition to the cyano group, while formation of

Scheme 4



compound **26a** may proceed *via* ring opening at C-2 of γ-pyrone to yield compound **24,** then cyclocondensation with the formyl group, while the isomeric form of compound **26b** is formed initially *via* condensation with the formyl group to afford compound **25,** then ring opening at C-2 of γ-pyrone.

EXPERIMENTAL

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. IR spectra were recorded on an FT-IR Bruker Vector 22 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were measured on a Gemini (200 MHz) spectrometer using DMSO-d_6 as solvent and TMS as an internal standard. Mass spectra were obtained using a Shimadzu GC-MS qp 1000 ex instrument mass spectrometer (70 eV). Elemental microanalyses were performed at the Cairo University Micro Analytical Center.

1,6-Diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (1) was prepared according to the reported method [26].

9-(4-Chlorophenyl)-2,4,7-trioxo-1,3,5,-trihydropyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (2). A mixture of compound **1** (1.46 g, 5 mmol) and diethyl malonate (0.8 ml, 5 mmol) in DMF (20 ml) was refluxed for 6 h; after cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed with water and recrystallized from DMF/H_2O to give compound **2** as white crystals, yield 0.92 g (63%); mp > 300ºC. IR spectrum, ν, cm^{-1}: 3415, 3343 (2NH); 2216, 2210 (2C≡N); 1668 (C=O pyridone); 1655-1645 (2C=O amide). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.35 (2H, s, CH_2); 5.67 (1H, s, NH); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 8.52 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 354 [M] (4.8), 321 (100). Found, %: C 54.85; H 2.42; Cl 10.3; N 19.55. $C_{16}H_8ClN_5O_3$. Calculated, %: C 54.43; H 2.26; Cl 10.02; N 19.80.

9-(4-Chlorophenyl)-2,7-dioxo-2,5-dihydropyrido[1,2-*b*][1,2,4]triazepine-4,8,10-tricarbonitrile (3). A mixture of compound **1** (1.46 g, 5 mmol) and ethyl ethoxymethylenecyanoacetate (0.56 g, 5 mmol) in DMF (20 ml) was refluxed for 6 h; after cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed with water, and crystallized from ethanol to give compound **3** as pale-yellow crystals, yield 0.85 g (58%); mp 280–282ºC. IR spectrum, ν, cm^{-1}: 3410, 3334 (2NH), 2226, 2220, 2218 (3C≡N); 1686 (C=O pyridone); 1655 (C=O amide). ^{1}H NMR, δ, ppm (*J*, Hz): 5.67 (1H, s, NH); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.79 (1H, s, H-3); 8.52 (1H, br. s, NH); Mass spectrum, *m/z* (*I*, %): 363 [M] (2.4). Found, %: C 56.65; H 3.42; Cl 9.57; N 21.35. $C_{17}H_7ClN_6O_2$. Calculated, %: C 56.27; H 1.93; Cl 9.79; N 23.17.

2-Amino-9-(4-chlorophenyl)-4-methylthio-7-oxo-5H-pyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile (5). A mixture of compound **1** (1.46 g, 5 mmol) and 2-cyano-3,3-bis(methylthio)acrylonitrile (0.85 g, 5 mmol) in DMF (20 ml) was refluxed for 4 h. The solid obtained after cooling was filtered off and recrystallized from DMF/EtOH to give compound **5** as yellow crystals, yield 1.2 g (82%); mp 210-212ºC. IR spectrum, ν, cm^{-1}: 3416, 3340, 3305 (NH, NH_2); 2978 (CH aliphatic); 2220, 2216, 2215 (3 C≡N); 1669 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66 (3H, s, SCH_3); 5.66 (1H, s, NH); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 8.51 (2H, s, NH_2). Found %: C 57.85; H 2.42; N 26.35; Cl 9.65. $C_{18}H_{10}ClN_7O$. Calculated, %: C 57.52; H 2.66; N 26.09; Cl 9.45.

Methyl 9-(4-chlorophenyl)-8,10-dicyano-2,7-dioxo-1,5-dihydropyrido[1,2-*b*][1,2,4]triazepine-4-carboxylate (6). A mixture of compound **1** (1.46 g, 5 mmol) and dimethyl acetylenedicarboxylate (0.83 ml, 5 mmol) in DMF (20 ml) was refluxed for 8 h. The solid obtained after cooling was filtered off and recrystallized from methanol to give compound **6** as brown crystals, yield 1.12 g (76%); mp 296–298ºC. IR spectrum, ν, cm^{-1}: 3412, 3344 (2NH); 2974 (CH aliphatic); 2220, 2216 (2C≡N); 1710 (CO ester); 1670 (C=O pyridone);

1646 (C=O amide). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.90 (3H, s, OCH_3); 5.67 (1H, s, NH); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.95 (1H, s, H-3); 8.53 (1H, s, NH). Found %: C 54.85; H 2.42; Cl 9.16; N 17.35. $C_{18}H_{10}ClN_5O_4$ (375.5). Calculated, %: C 54.61; H 2.52; Cl 8.97; N 17.69.

9-(4-Chlorophenyl)-2,4-dimethyl-7-oxo-3,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (8). A mixture of compound **1** (1.46 g, 5 mmol) and acetylacetone (0.5 ml, 5 mmol) in glacial acetic acid (30 ml) was refluxed for 6 h; after cooling the reaction mixture was poured onto ice. The solid obtained was filtered off, washed with water, and crystallized from methanol to give compound **8** as white crystals, yield 1.0 g (68%); mp 290–291ºC. Reported mp 298ºC [24].

9-(4-Chlorophenyl)-2,4-dimethyl-7-oxo-3-phenylhydrazono-1H-pyrido[1,2-*b*][1,2,4]triazepine-8,10-tricarbonitrile (9). A. A mixture of compound **1** (1.46 g, 5 mmol) and 3-phenylazo-2,4-pentanedione (**7**) (1.02 g, 5 mmol) in acetic acid (20 ml) was refluxed for 8 h. The solid obtained after cooling was filtered off and recrystallized from methanol to give compound **9** as orange crystals, yield 1.10 g (75%); mp 275-276ºC.

B: A mixture of compound **8** (0.57 g, 7 mmol) in ethanol (25 ml) and sodium acetate (1 g) was added gradually to a solution of benzene diazonium chloride (0.51 g, 4 mmol); the temperature was kept lower than 5ºC. The solid obtained was filtered off and recrystallized from DMF/MeOH to give compound **9** as orange crystals, yield 1.22 g (83%); mp 275–276ºC. IR spectrum, ν, cm^{-1}: 3304 (NH); 2987 (CH aliphatic); 2220, 2216 (2C≡N); 1670 (C=O); 1520 (N=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 2.47 (3H, s, CH_3); 7.22, 7.24 (2H, d, *J* = 8.2, Ar); 7.46–7.59 (5H, m, C_6H_5); 7.61, 7.66 (2H, d, *J* = 8.2, Ar); 8.52 (1H, s, NH). Found, %: C 63.85; H 3.42; Cl 7.61; N 21.35. $C_{24}H_{16}ClN_7O$. Calculated, %: C 63.50; H 3.52; Cl 7. 82; N 21.60.

8-(4-Chlorophenyl)-2,6-dioxo-1H-pyrido[1,2-*b*][1,2,4]triazine-3,7,9-tricarbonitrile (11). A mixture of compound **1** (1.46 g, 5 mmol) and ethyl α-cyano-α-phenylazoacetate (1.08 g, 5 mmol) in acetic acid (20 ml) was refluxed for 4 h; after cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off and recrystallized from DMF/H_2O to give compound **11** as yellow crystals, yield 1.25 g (85%); mp 311-312ºC. IR spectrum, ν, cm^{-1}: 3415 (NH); 2220, 2215, 2210 (3C≡N); 1669 (C=O pyridone); 1653 (C=O amide). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22 (1H, s, H-3); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 8.51 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 348 (13.0), 63 (100). Found %: C 54.85; H 1.42; Cl 10.37; N 24.35. $C_{16}H_5ClN_6O_2$. Calculated, %: C 55.09; H 1.43; Cl 10.18; N 24.10.

2-(2-Benzoylaminophenyl)-7-(4-chlorophenyl)-5-oxo-1H-[1,2,4]triazolo[2,3-*a*]pyridine-6,8-dicarbonitrile (15). A mixture of compound **1** (1.46 g, 5 mmol) and 2-phenyl-4H-3,1-benzoxazin-4-one (0.56 g, 5 mmol) in dry pyridine (30 ml) was refluxed for 6 h; after cooling, the reaction mixture was poured onto ice-HCl. The solid obtained was filtered off, washed with water, and recrystallized from DMF/H_2O to give compound **15** as yellow crystals, yield 0.96 g (61%); mp 250-252ºC. IR spectrum, ν, cm^{-1}: 3410, 3315 (2NH); 2222, 2216 (2 C≡N); 1668 (C=O pyridone); 1345 (C=O amide). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22-7.26 (4H, m, C_6H_4); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.95–8.09 (5H, m, C_6H_5); 8.56 (1H, s, NH); 12.18 (1H, s, NH). Found, %: C 65.85; H 3.12; Cl 7.39; N 17.35. $C_{27}H_{15}ClN_6O_2$. Calculated, %: C 66.05; H 3.05; Cl 7.23; N 17.12.

10-(4-Chlorophenyl)-4-hydroxy-2,6-dimethyl-8-oxopyrano[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazepine-9,11-dicarbonitrile (19). A mixture of compound **1** (1.46 g, 5 mmol) and dehydroacetic acid (0.84 ml, 5 mmol) in glacial acetic acid (40 ml) was refluxed for 8 h; after cooling, the reaction mixture was poured onto ice. The solid obtained was filtered off, washed with water and recrystallized from DMF to give compound **19** as brown crystals, yield 1.24 g (85%); mp 308–309ºC. IR spectrum, ν, cm^{-1}: 3535 (OH); 3395, 3325 (2NH); 2987 (CH aliphatic); 2221, 2216 (2 C≡N); 1655 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (3H, s, CH_3); 3.34 (3H, s, CH_3); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.95 (1H, s, H-3); 8.50 (1H, s, OH). Mass spectrum, *m/z* (*I*, %): 417 [M] (17.9), 77 (100). Found, %: C 60.65; H 2.62; Cl 8.79; N 16.55. $C_{21}H_{12}ClN_5O_3$. Calculated, %: C 60.35; H 2.87; Cl 8.50; N 16.76.

2-Amino-9-(4-chlorophenyl)-3-(2-hydroxybenzoyl)-7-oxo-6H-pyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (23). A mixture of compound **1** (1.46 g, 5 mmol) and chromone-3-carbonitrile (**20**) (0.85 g,

5 mmol) in dry pyridine (40 ml) was refluxed for 4 h; after cooling, the reaction mixture was poured onto ice-HCl. The solid obtained was filtered off and recrystallized from DMF/H_2O to give compound **23** as yellow crystals, yield 1.35 g (92%); mp 262-264ºC. IR spectrum, ν, cm^{-1}: 3527 (OH); 3453, 3397, 3304 (NH, NH_2); 2220, 2219 (2 C≡N); 1668 (C=O); 1655 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.67 (2H, s, NH_2); 7.32 (1H, s, H-4); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.97–8.09 (4H, m, C_6H_4); 8.52 (1H, s, NH); 9.12 (1H, s, OH). Found, %: C 60.85; H 2.62; Cl 7.97 N 18.35. $C_{23}H_{13}ClN_6O_3$. Calculated, %: C 60.46; H 2.84; Cl 7.77; N 18.40.

9-(4-Chlorophenyl)-3-(2-hydroxybenzoyl)-7-oxo-6H-pyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (26). A mixture of compound **1** (1.46 g, 5 mmol) and chromone-3-carbaldehyde (**21**) (0.87 g, 5 mmol) in dry pyridine (40 ml) was refluxed for 4 h; after cooling, the reaction mixture was poured onto ice-HCl. The solid obtained was filtered off and crystallized from DMF/H_2O to give compound **26** as yellow crystals, yield 1.18 g (80%); mp 157-158ºC. IR spectrum, ν, cm^{-1}: 3527 (OH); 3305 (NH); 2221, 2216 (2 C≡N); 1668 (C=O pyridone); 1655 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.06 (1H, s, H-4); 7.30 (1H, s, H-2); 7.51, 7.55 (2H, d, *J* = 8.2, Ar); 7.62, 7.66 (2H, d, *J* = 8.2, Ar); 7.97–8.09 (4H, m, C_6H_4); 8.20 (1H, s, NH); 8.94 (1H, s, OH). Found %: C 62.85; H 2.42; Cl 8.32; N 15.55. $C_{23}H_{12}ClN_5O_3$. Calculated, %: C 62.51; H 2.71; Cl 8.04; N 15.85.

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