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Synthesis and Antibacterial Acivity of Some Novel Pyrimidine-Based Heterocycles

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Abstract—Cyclization of 1,2-diamino-4(4-chlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **2** with a variety of electrophilic reagents results in formation of a new series of pyrimidine heterocycles including pyrimidotriazepines, pyrimidotriazines and triazolopyrimidines. Some newly synthesized compounds are tested for their antibacterial activity against Gram-positive and Gram-negative bacteria.

Keywords: pyrimidotriazepine, pyrimidotriazine, triazolopyrimidine, cyclocondensation, heterocyclization

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INTRODUCTION

According to literature survey many condensed pyrimidines act as antibacterial [1-3], antifungal [4, 5], analgesic [6], anticonvulsant [7], antihistaminic [8], antidiabetic [9], anti-inflammatory [10], antiviral [11], antioxidant [12], and anticancer agents [13].

In continuation of our earlier efforts [14, 15] in synthesis of novel heterocycles with potential biological activity, we report herein a synthetic approach to a new series of pyrimidine heterocycles based on 1,2-diamino-4(4-chlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **2**. Some of new compounds demonstrated promising antibacterial activity against Gram-positive and Gram-negative bacteria.

RESULTS AND DISCUSSION

In the current study synthetic approach to a new series of pyrimidine heterocycles was based on 1,2-diamino-4(4-chlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **2** which had been synthesized by hydrazinolysis of methylthiopyrimidone derivative **1** [16].

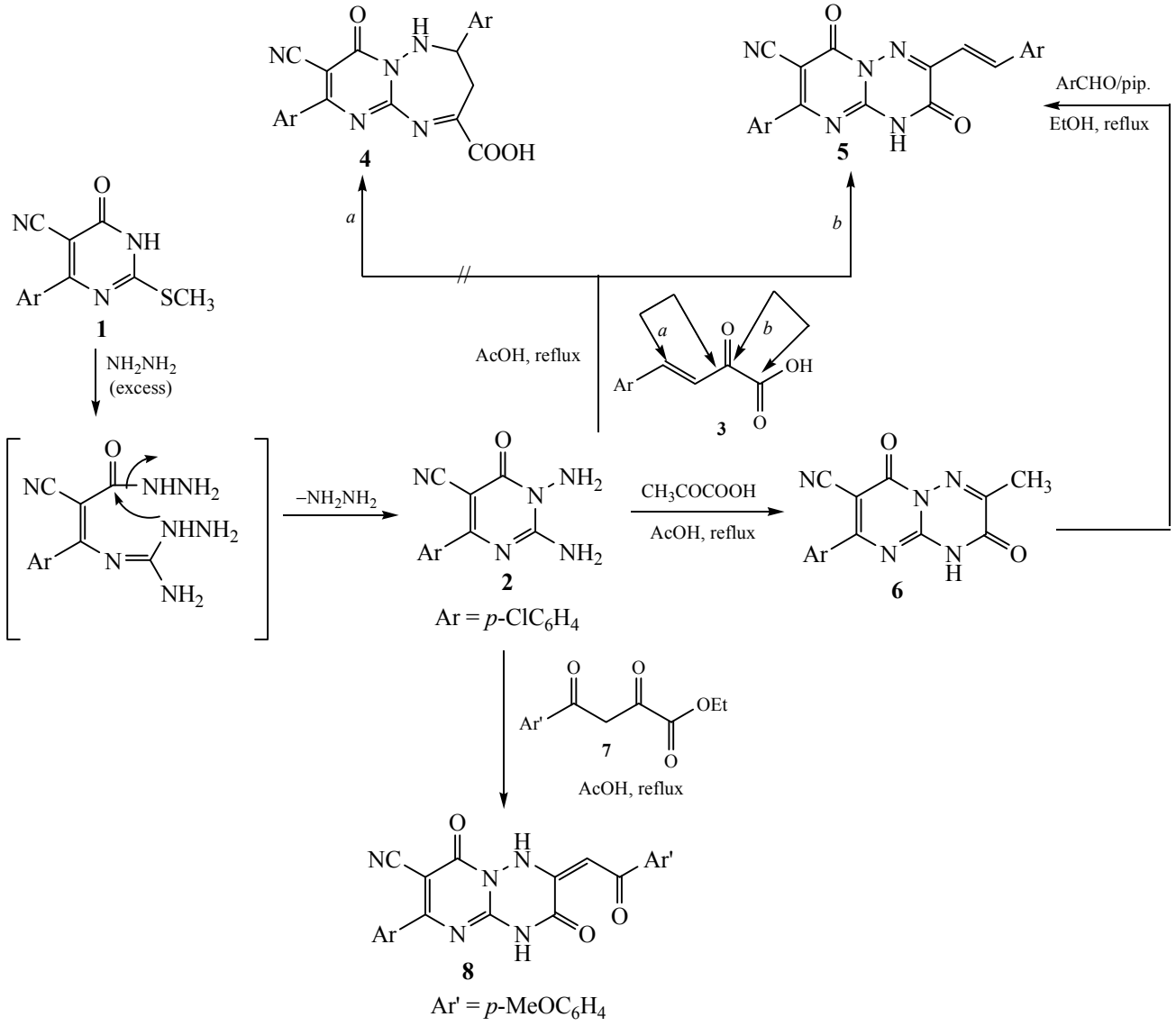
Refluxing of compound **2** with 4-(4-chlorophenyl)-2-oxobut-3-enoic acid **3** did not give the expected pyrimidotriazepine **4** but resulted in formation of pyrimidotriazine **5** in moderate yield (Scheme 1). ^{1}H NMR spectrum of compound **5** contained a singlet at 12.60 ppm typical for NH and multiplet signals in the range of 6.96 to 8.01 ppm attributed to Ar-H and olefinic-H. IR spectrum of compound **5** displayed the bands at 1655 cm^{-1} (C=O) and 2217 cm^{-1} (C≡N).

Treatment of pyrimidotriazine **6** (obtained by cyclocondensation of **2** with pyruvic acid) by *p*-chlorobenzaldehyde in the presence of piperidine led to the same product **5**.

Pyrimidotriazine **8** was obtained via reaction of compound **2** with ethyl 4-(4-methoxyphenyl)-2,4-dioxobutanoate **7** upon refluxing in acetic acid (Scheme 1). ^{1}H NMR spectrum indicated formation of compound **8** by singlets at 3.82 ppm (OCH_3), 11.50 ppm (NH) and 12.06 ppm (NH).

Scheme 2 illustrates further heterocyclizations of compound **2** with different carbonyl reagents (isatin, maleic anhydride and phenacyl bromide) with formation of the corresponding pyrimidotriazine derivatines **9**-**11**. The structures of these compounds were supported by the spectral data. For example, ^{1}H NMR spectrum of compound **10** revealed the presence of four singlets at 1.92, 10.07, 10.35, and 12.42 ppm attributed to triazine-CH_3, two NH and OH groups, respectively. ^{1}H NMR spectrum of compound **11** displayed two singlets at 4.95 ppm (triazine-CH_2) and 12.25 ppm (NH). Compound **10** may be formed via initial nucleophilic attack of the N-NH_2 functional group of compound **2** on the electrophilic carbonyl carbon of maleic anhydride followed by triazine cyclization and subsequent decarboxylation as illustrated by Scheme 3. The three-component reaction of diaminopyrimidine **2** with diethyl malonate and benzaldehyde in presence of sodium acetate in acetic

Scheme 1. Synthetic approach to pyrimidotriazine derivatives **5, 6** and **8**.



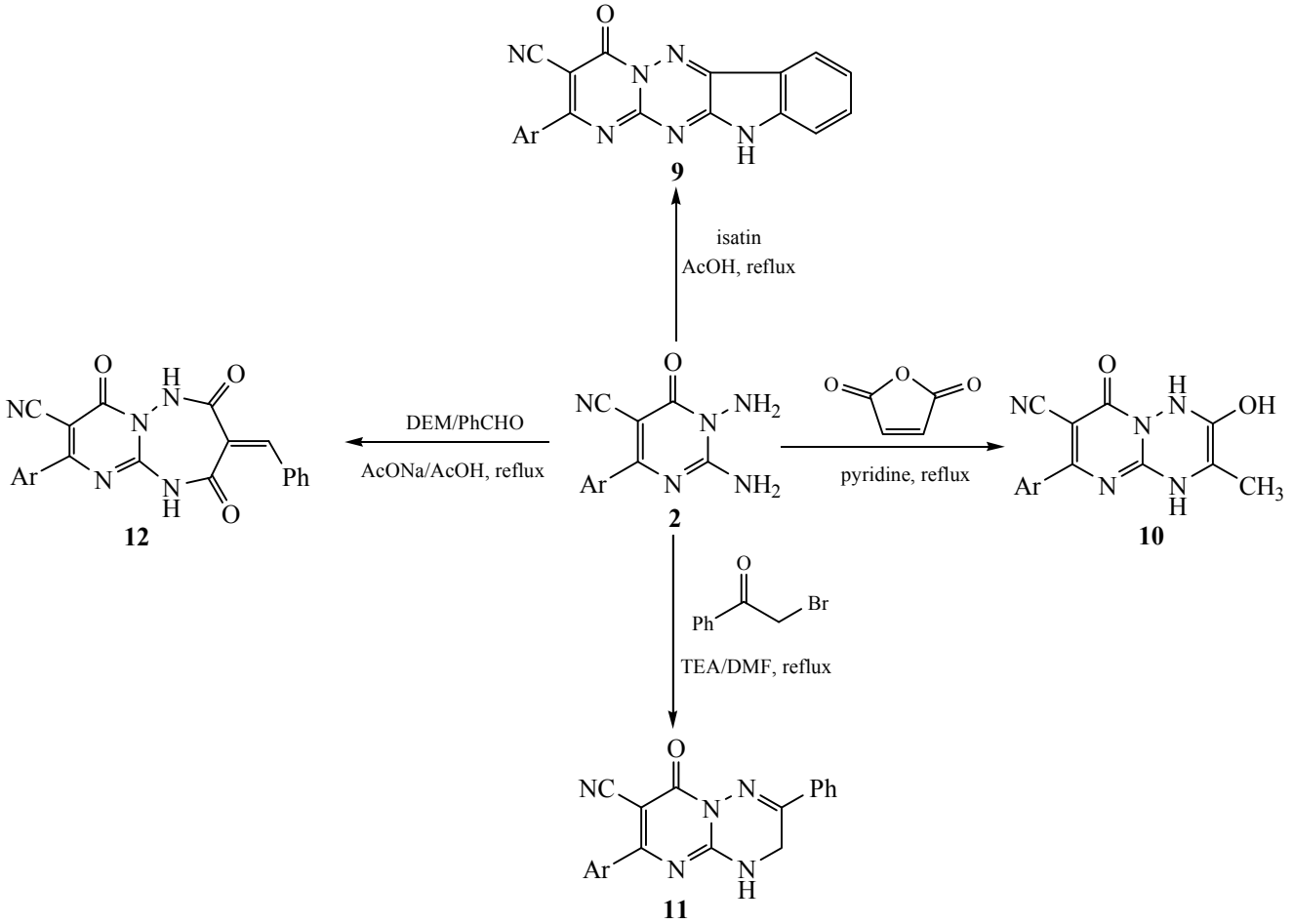
acid resulted in formation of pyrimidotriazepine **12** in high yield. ^{1}H NMR spectrum of compound **12** demonstrated a singlet of vinylic-H (8.19 ppm) and two singlets at 12.47 and 12.62 ppm attributed to two NH protons (Scheme 3).

In attempt to synthesize pyrimidotriazepine **13**, diaminopyrimidine **2** was treated with benzylidene malonotrile upon refluxing in pyridine. However, the isolated product was identified as pyrimdotriazepine **12**, which could be formed upon hydrolysis of the intermediate **14**.

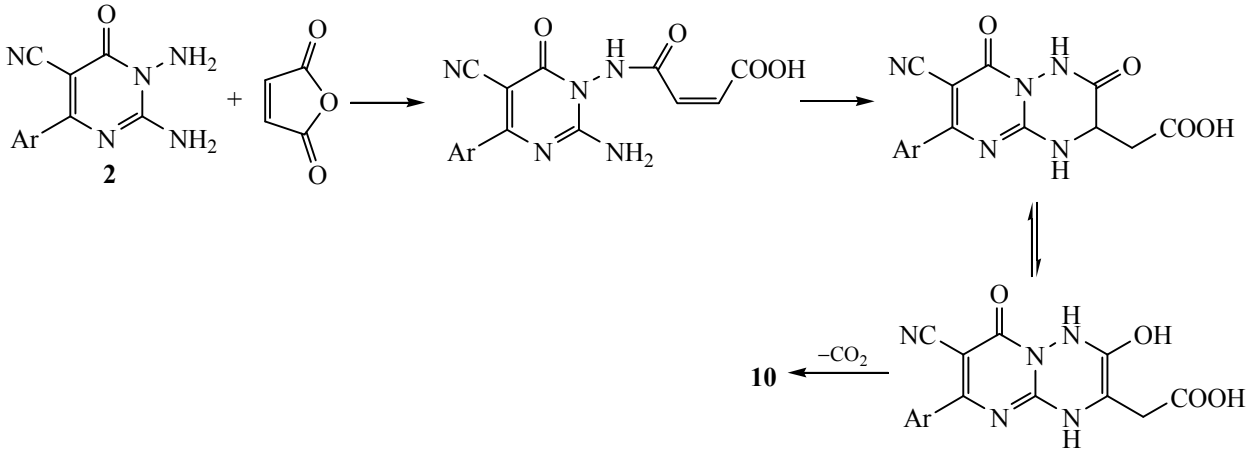
1,2-Diaminopyrimidine **2** could be functionalized also for construction of some triazolopyrimidines. Thus, treatment of compound **2** with benzoyl isothiocyanate, furan-2-carbonylchloride or acetic anhydride gave the corresponding triazolopyrimidines **15-17**. The structures of these compounds were deduced from the spectral data. For example, ^{1}H NMR spectrum of compound **17** demonstrated two singlets at 2.34 and 2.67 ppm typical for CH_3 groups. This was supported by the ^{13}C NMR spectrum which exhibited two sp^3 signals at 24.90 and 25.92 ppm. IR spectrum of **17** displayed the bands at 2226 and 1690 cm^{-1} typical for C≡N and C=O functional groups, respectively (Scheme 4).

Antibacterial activity. Compounds **5**, **8**, **10**, **12,** and **17** were tested in vitro for antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*,

Scheme 2. Synthetic route for pyrimidotriazines **9-11** and pyridopyrimidotriazine **12**.

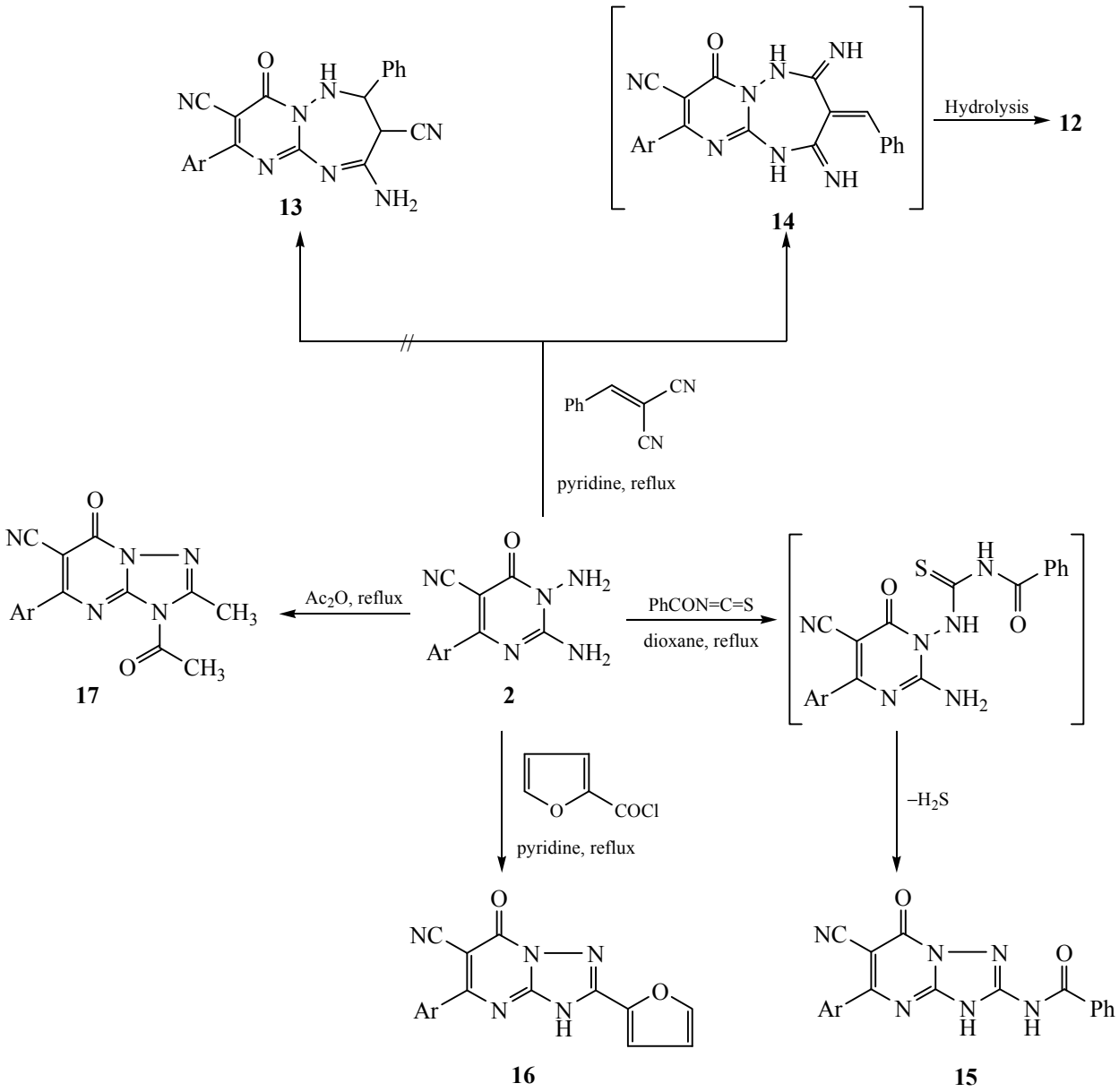


Scheme 3. Pathway to pyrimidotriazine **10**.



Staphylococcus aureus) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) using the disc diffusion method [17] at 1 mg/mL concentration (see the table). Ampicillin was used as a standard. DMSO was used as a solvent. The zones of inhibition of bacterial growth were observed.

Scheme 4. Synthetic route for triazolopyrimidines **15**–**17**.



According to the accumulated data, the tested compounds exhibited moderate to good antibacterial activity, particularly compound **10**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on an Unicam SP 1200G spectrophotometer. ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were measured on a Bruker spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) using TMS as an internal standard. NMR spectra were measured at Micro Analytical Unit, Faculty of Pharmacy, Cairo University. Elemental analyses and IR spectroscopy were carried out at Micro Analytical Center, Cairo University.

6-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)ethenyl]-3,8-dioxo-4,8-dihydro-3*H*-pyrimido[1,2-*b*][1,2,4]-triazine-7-carbonitrile (5). *a.* A mixture of compound **2** (0.01 mol) with 4-(4-chlorophenyl)-2-oxobut-3-enoic acid **3** (0.01 mol) in acetic acid (50 mL) was refluxed

In vitro antibacterial activity for a group of the synthesized compounds

Sample	Inhibition zone diameter, mm/mg			
	bacterial species			
	gram+		gram–	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
Control: DMSO	0.0	0.0	0.0	0.0
Ampicillin	26	21	25	26
5	14	14	15	14
8	11	11	12	12
10	25	22	23	21
12	13	16	15	12
17	20	19	17	19

for 5 h. The solid formed was filtered off while hot, dried and recrystallized from DMF to give compound **5** as pale red crystals.

b. A mixture of compound **6** (0.01 mol) with *p*-chlorobenzaldehyde (0.01 mol) and catalytic amount of piperidine in DMF (20 mL) was refluxed for 3 h. Upon completion of the process, the reaction mixture was cooled down. The precipitate was filtered off, dried and recrystallized from DMF to give product **5** as pale red crystals. Yield 68% (*a*), 77% (*b*), mp 258–260°C. IR spectrum, ν, cm^{-1}: 3446 (NH), 2217 (C≡N), 1655 (C=O). ^{1}H NMR, spectrum, δ, ppm: 6.96–8.01 m (10H, Ar-H + olefinic-H), 12.60 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 88.91, 116.93, 123.70, 125.89, 128.96, 129.05, 130.63, 130.77, 134.00, 134.13, 136.41, 153.18, 153.76, 161.65, 164.49, 168.55, 170.23. Found, %: C 57.95, H 2.46, N 16.19. $C_{21}H_{11}Cl_2N_5O_2$. Calculated, %: C 57.82, H 2.54, N 16.05.

6-(4-Chlorophenyl)-2-methyl-3,8-dioxo-4,8-dihydro-3*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (6). A mixture of compound **2** (0.01 mol) with pyruvic acid (0.01 mol) in acetic acid (50 mL) was refluxed for 3 h. The reaction mixture was then cooled down and the precipitate was filtered off, dried and recrystallized from acetic acid to give compound **6** as white crystals.Yield 83%, mp 276–278°C. IR spectrum, ν, cm^{-1}: 3418 (NH), 2217 (C≡N), 1687 (C=O). ^{1}H NMR, spectrum, δ, ppm: 2.16 s (3H, CH_3), 7.64–7.92 m (4H, Ar-H), 12.18 s (1H, NH). ^{13}C NMR, spectrum, δ, ppm: 13.13, 89.44, 116.80, 128.99, 130.76, 134.87, 136.67, 154.37, 161.86, 164.60, 169.78, 172.55. Found, %: C 53.49, H 2.66, N 22.45. $C_{14}H_8ClN_5O_2$. Calculated, %: C 53.60, H 2.57, N, 22.32.

6-(4-Chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxoethylidene]-3,8-dioxo-2,3,4,8-tetrahydro-1*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (8). A mixture of compound **2** (0.01 mol) with ethyl 4-(4-methoxyphenyl)-2,4-dioxobutanoate **7** (0.01 mol) in acetic acid (50 mL) was refluxed for 3 h, then it was cooled down, poured into cold water, and the solid formed was filtered off, dried and recrystallized from ethanol to give compound **8** as yellow crystals. Yield 87%, mp 274–276°C. IR spectrum, ν, cm^{-1}: 3444, 3299 (NH), 2213(C≡N), 1662 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 6.96–8.11 m (9H, Ar-H + exocyclic vinylic-H), 11.50 s (1H, NH), 12.06 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 55.72, 86.84, 113.92, 115.21, 117.46, 128.91, 129.38, 129.88, 130.69, 135.43, 136.33, 154.46, 161.17, 161.89, 165.13, 166.00, 169.88. 171.25. Found, %: C 59.13, H 3.07, N 15.55. $C_{22}H_{14}ClN_5O_4$. Calculated, %: C 59.00, H 3.15, N 15.64.

8-(4-Chlorophenyl)-6-oxo-6,11-dihydro-5,5a,9,10,11-pentaazabenzo[*b*]fluorine-7-carbonitrile (9). A mixture of compound **2** (0.01 mol) with isatin (0.01 mol) in acetic acid (30 mL) was refluxed for 5 h. The solid formed was filtered off while hot, dried and recrystallized from DMF to give compound **9** as yellow crystals. Yield 74%, mp > 300°C. IR spectrum, ν, cm^{-1}: 3423 (NH), 2218(C≡N), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.28–8.24 m (8H, Ar-H), 11.32 s (1H, NH). ^{13}C NMR spectrum could not be

accumulated because of low solubility of the compound in common solvents used in NMR spectroscopy. Found, %: C 61.31, H 2.55, N 22.40. $C_{19}H_9ClN_6O$. Calculated, %: C 61.22, H 2.43, N 22.54.

6-(4-Chlorophenyl)-2-hydroxy-3-methyl-8-oxo-4,8-dihydro-1*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (10). A mixture of compound **2** (0.01 mol) with maleic anhydride (0.01 mol) in dry pyridine (20 mL) was refluxed for 6 h. The reaction mixture was then cooled down, poured into cold water and neutralized with dil. HCl. The solid formed was filtered off, dried and recrystallized from ethanol to give compound **10** as reddish brown crystals. Yield 79%, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3448, 3244 (OH, NH), 2220 (C≡N), 1657 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 7.59–7.86 m (4H, Ar-H), 10.07 s (1H, NH), 10.35 s (1H, NH), 12.42 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 13.87, 83.04, 86.25, 117.28, 128.84, 129.41, 130.76, 135.34, 144.59, 162.50, 168.35, 170.45. Found, %: C 53.37, H 3.06, N 22.29. $C_{14}H_{10}ClN_5O_2$. Calculated, %: C 53.26, H 3.19, N 22.18.

6-(4-Chlorophenyl)-8-oxo-2-phenyl-4,8-dihydro-3*H*-pyrimido[1,2-*b*][1,2,4]triazine-7-carbonitrile (11). A mixture of compound **2** (0.01 mol) with phenacyl bromide (0.01 mol) and catalytic amount of TEA in DMF (20 mL) was refluxed for 3 h. The reaction mixture was then cooled down, poured into cold water, and the solid formed was filtered off, dried and recrystallized from ethanol to give compound **11** as green crystals. Yield 80%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 3397 (NH), 2215(C≡N), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.95 s (2H, CH_2), 7.42–7.89 m (9H, Ar-H), 12.25 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 45.32, 87.82, 116.88, 128.85, 129.11, 129.30, 130.57, 131.17, 133.30, 134.92, 136.72, 156.88, 162.06, 164.19, 168.32. Found, %: C 63.19, H 3.25, N 19.49. $C_{19}H_{12}ClN_5O$. Calculated, %: C 63.08, H 3.34, N 19.36.

3-Benzylidene-7-(4-chlorophenyl)-2,4,9-trioxo-1,2,3,4,5,9-hexahydropyrimido[1,2-*b*][1,2,4]triazepine-8-carbonitrile (12). A mixture of DEM (0.01 mol) with benzaldehyde (0.01 mol) and fused sodium acetate (0.01 mol) in acetic acid (10 mL) was refluxed for 5 min, then a solution of compound **2** (0.01 mol) in acetic acid (40 mL) was added, and the reaction mixture was refluxed for 3 h. Upon completion of the process, the reaction mixture was cooled down, poured into cold water and the solid formed was filtered off, dried and recrystallized from ethanol to give compound **12** as white crystals. Yield 84%, mp > 300°C. IR spectrum, ν, cm^{-1}: 3436 (NH), 2214 (C≡N), 1657 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.44–8.04 m (9H, Ar-H), 8.19 s (1H, exocyclic vinylic-H), 12.47 s (1H, NH), 12.62 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 87.09, 117.42, 126.20, 128.56, 128.94, 128.99, 130.64, 130.90, 134.07, 135.40, 136.38, 147.77, 160.99, 162.05, 165.00, 169.79, 171.10 Found, %: C 60.49, H 2.79, N 16.63. $C_{21}H_{12}ClN_5O_3$. Calculated, %: C 60.37, H 2.89, N 16.76.

***N*-[5-(4-Chlorophenyl)-6-cyano-7-oxo-3,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl]benzamide (15).** A mixture of compound **2** (0.01 mol) with benzoyl isothiocyanate (0.01 mol) in dioxane (60 mL) was refluxed for 3 h, then it was cooled down, poured into cold water and the precipitated product was filtered off, dried and recrystallized from ethanol to give compound **15** as yellow crystals. Yield 62%, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3448, 3226 (NH), 2211 (C≡N), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.74–8.04 m (9H, Ar-H), 9.91 s (1H, NH), 10.62 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 83.99, 116.29, 127.30, 128.63, 128.83, 128.96, 130.52, 130.63, 135.79, 136.12, 155.71, 161.84, 164.17, 168.55. 170.27. Found, %: C 58.29, H 2.91, N 21.43. $C_{19}H_{11}ClN_6O_2$. Calculated, %: C 58.40, H 2.84, N 21.51.

5-(4-Chlorophenyl)-2-(furan-2-yl)-7-oxo-3,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (16). A mixture of compound **2** (0.01 mol) with furan-2-carbonylchloride (0.01 mol) in dry pyridine (20 mL) was refluxed for 6 h, then it was cooled down, poured into cold water and neutralized with dil. HCl. The solid formed was filtered off, dried and recrystallized from ethanol to give compound **16** as pale yellow crystals. Yield 65%, mp 296–298°C. IR spectrum, ν, cm^{-1}: 3431 (NH), 2215 (C≡N), 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.69–7.94 m (7H, Ar-H), 10.62 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 86.37, 112.44, 115.70, 117.35, 128.60, 128.97, 130.60, 135.35, 146.22, 146.62, 158.19, 162.89, 164.11, 170.09. Found, %: C 56.79, H 2.50, N 20.65. $C_{16}H_8ClN_5O_2$. Calculated, %: C 56.90, H 2.39, N 20.74.

3-Acetyl-5-(4-chlorophenyl)-2-methyl-7-oxo-3,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (17). A mixture of compound **2** (0.01 mol) with acetic anhydride (30 mL) was refluxed for 3 h, then it was cooled down, and the solid precipitate was filtered off, dried and recrystallized from ethanol to give

compound **17** as white crystals. Yield 65%, mp 296–298°C. IR spectrum, ν, cm^{-1}: 2226 (C≡N), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 2.67 s (3H, CH_3), 6.68–7.94 m (4H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 24.90, 25.92, 90.40, 115.65, 129.05, 129.39, 130.69, 134.32, 156.46, 168.76, 170.90, 171.22, 172.56. Found, %: C 54.86, H 2.96, N 21.50. $C_{15}H_{10}ClN_5O_2$. Calculated, %: C 54.97, H 3.08, N 21.37.

CONCLUSIONS

A series of novel condensed pyrimidines are synthesized upon cyclization of 1,2-diaminopyrimidine derivative with various reagents. Some of the newly synthesized compounds demonstrate pronounced antibacterial activity against the tested microorganisms.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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