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Synthesis and antimicrobial activities of pyrido[2,3-*d*]pyrimidine, pyridotriazolopyrimidine, triazolopyrimidine, and pyrido[2,3-*d*:6,5*d*']dipyrimidine derivatives

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ABSTRACT

A new series of pyridotriazolopyrimidines were synthesized via reaction of hydrazonoyl halides with pyrido[2,3-*d*]pyrimidines. The structures of the newly synthesized compounds were established by elemental analysis, spectral data and alternative synthetic routes whenever possible. Some of synthesized compounds were also screened in vitro for their antimicrobial activity against a variety of bacterial and fungal samples.

1. Introduction

Previously, it was reported that pyrido[2,3-*d*]pyrimidines possess abroad spectrum of biological activity. They are used as antiallergic [1], antiasmatic agents [2], antihypertensive [3], anti-inflammatory [4], anticancer and antiviral [5-8], diuretic [9] and anticancer agents [10,11]. Other than their biological importance, they are valuable for synthesis of polyfunctional heterocyclic compounds. As an extension of our study [12-18] and our program aiming at the synthesis of different heterocyclic derivatives, we report herein the convenient synthesis of some new triazolo[4,3-*a*]pyrimidin-5(*H*)-one, pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one and 1,2,4-triazolino[4,5-*a*]-1,2,4-triazolino[4'',5''-1',2']pyrimidino[5',4'-5,6]pyridino[2,3-*d*]pyrimidin-4,6-dione derivatives.

2. Experimental

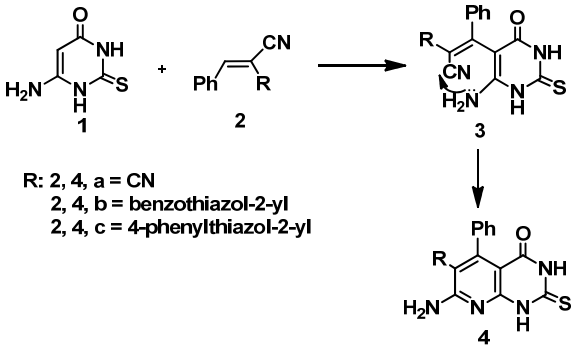
2.1. Instrumentation

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in δ ppm units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Micro analytical Center of Cairo University. Hydrazonoyl halides **5a-e** [19-23] were prepared as previously reported.

2.2. Synthesis

2.2.1. Synthesis of pyrido[2,3-d] pyrimidines (4a-c)

A mixture of equimolecular amounts of 6-amino-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one [24] (**1**) (5 mmol) and the appropriate of 2-benzylidenemalononitrile (**2a**), 2-(benzo[*d*]thiazol-2-yl)3-phenylacrylonitrile (**2b**) and 3-phenyl-2-(4-phenylthiazol-2-yl) acrylonitrile (**2c**) (5 mmol) in absolute ethanol (10 mL) containing triethylamine (3 drops) was heated under reflux for 3 h. The reaction mixture was concentrated and cooled. The solid obtained was filtered off, washed with ethanol and recrystallized from *N,N*-dimethylformamide to give **4a-c**, respectively (Scheme 1).



Scheme 1

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7-Amino-1,2,3,4-tetrahydro-4-oxo-5-phenyl-2-thioxopyrido [2,3-d]pyrimidine-6-carbonitrile (**4a**) [25]**:** Color: Pale yellow (from *N,N*-dimethylformamide). Yield: 80%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3439, 3320 (NH_2, NH), 3058 (CH, aromatic), 2214 (CN), 1639 (CO), 1616 (C=N), 1527 (C=C). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.72 (s., br., 2H, NH_2), 7.42-7.40 (m, 7H, ArH's and NH). Anal. calcd. for $C_{14}H_9N_5OS$: C, 56.94; H, 3.07; N, 23.71; S, 10.86. Found: C, 57.11; H, 3.14; N, 23.85; S, 11.00%.

7-Amino-4-oxo-5-phenyl-6-(benzo[d]thiazol-2-yl)-2-thioxo-1, 2,3,4-tetrahydro pyrido[2,3-d]pyrimidine (**4b**): Color: Pale yellow (from *N,N*-dimethylformamide). Yield: 80%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3250 (brs, NH), 3058 (CH, aromatic), 1639 (C=O), 1616 (C=N), 1527 (C=C). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 5.78 (s, br, 2H, NH_2), 6.74-7.13 (m, 10H, ArH's, NH), 12.01 (s, 1H, NH). Anal. calcd. for $C_{20}H_{13}N_5OS_2$: C, 59.54; H, 3.25; N, 17.36; S, 15.89. Found: C, 59.49; H, 3.30; N, 17.40 S, 15.95%.

7-Amino-4-oxo-5-phenyl-6-(phenylthiazol-2-yl)-2-thioxo-1,2, 3,4-tetrahydro pyrido[2,3-d]pyrimidine (**4c**): Color: Orange (from *N,N*-dimethylformamide). Yield: 80%. M.p.: 230-232 °C. FT-IR (KBr, ν, cm^{-1}): 3301, 3224, 3136 (NH, NH_2), 3070 (CH, aromatic), 1697 (C=O), 1627 (C=N), 1593 (C=C). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.88-6.91 (s, br., 2H, NH_2), 7.22-7.81 (m, 12H, ArH's, thiazole H-5, NH and NH_2), 13.00 (s, 1H, NH). Anal. calcd. for $C_{22}H_{15}N_5OS_2$: C, 61.52; H, 3.52; N, 16.31; S, 14.93. Found: C, 61.45; H, 3.47; N, 16.26; S, 15.00%.

2.2.2. Synthesis of compounds 10a-e, 11a-e and 12a-d

Method A: A mixture of the appropriate **4a-c** (5 mmol), the appropriate hydrazonoyl halides **5a-e** (5 mmol) and triethylamine (5 mmol) in chloroform were heated under reflux for 10 hrs. The excess solvent was evaporated and the residue was triturated with ethanol (10 mL). The solid formed was filtered off and crystallized from a proper solvent to give **10**-**12**, respectively (Scheme 2).

Method B: Equimolar amounts of the appropriate **4a-c** (5 mmol), the appropriate hydrazonoyl halides **5a-e** (5 mmol) and sodium ethoxide (5 mmol) in ethanol (20 mL) were refluxed for 3 h. The reaction mixture was cooled; the resulting solid was collected and recrystallized from a proper solvent to give products identical in all aspects (M.p., mixed m.p., and spectra) with the corresponding products obtained by method A (Scheme 2).

8-Amino-3-(benzofuran-2-yl-carbonyl)-7-cyano-5-oxo-1,6-di-phenyl-1,5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine (**10a**): Color: Red (from ethanol). Yiled: 82%. M.p.: 148-150 °C. FT-IR (KBr, ν, cm^{-1}): 3300, 3197 (NH_2), 3055 (CH, aromatic), 2214 (CN), 1650 (C=O), 1612 (C=N), 1531 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.28 (s, br., 2H, NH_2), 7.15-8.21 (m, 15H, ArH's). Anal. calcd. for $C_{30}H_{17}N_7O_3$: C, 68.83; H, 3.27; N, 18.73. Found: C, 68.73; H, 3.20; N, 18.60%.

Ethyl 8-amino-7-cyano-5-oxo-1,6-diphenyl-1,5-dihydropyrido [2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (**10b**): Color: White (from acetic acid). Yield: 75%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3295, 3190 (NH_2), 3062 (CH, aromatic), 2221 (CN) 1751, 1716 (C=O), 1620 (C=N), 1546 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.21 (t, 3H, *J* = 7.5 Hz, CH_3), 4.37 (q, 2H, *J* = 7.5 Hz, CH_2), 7.33-8.14 (m, 12H, ArH's+NH_2). Anal. calcd. for $C_{24}H_{17}N_7O_3$: C, 63.85; H, 3.80; N, 21.72. Found: C, 63.78; H, 3.88; N, 21.65%.

8-Amino-3-acetyl-7-cyano-5-oxo-1,6-diphenyl-1,5-dihydro pyrido[2,3-d][1,2,4]triazolo-[4,3-a]pyrimidine (**10c**): Color: Red (from ethanol). Yield: 75%. M.p.: 180-182 °C. FT-IR (KBr, ν, cm^{-1}): 3336, 3205 (NH_2), 3062 (CH, aromatic), 2214 (CN) 1665, 1650 (C=O), 1612 (C=N), 1531 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.73 (s, 3H, $COCH_3$), 7.12-7.48 (m, 12H, ArH's and NH_2). Anal. calcd. for $C_{23}H_{15}N_7O_2$: C, 65.55; H, 3.59; N, 23.27. Found: C, 65.61; H, 3.51; N, 23.20%.

8-Amino-3-benzoyl-7-cyano-5-oxo-1,6-diphenyl-1,5-dihydro pyrido[2,3-d][1,2,4]triazolo-[4,3-a]pyrimidine (**10d**): Color: Red (from ethanol). Yield: 78%. M.p.: 189-190 °C. FT-IR (KBr, ν, cm^{-1}): 3332, 3182 (NH_2), 3062 (CH, aromatic), 2218 (CN), 1640 (C=O), 1624 (C=N), 1546 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.44 (s, br., 2H, NH_2), 7.25-8.06 (m, 15H, ArH's). Anal. calcd. for $C_{28}H_{17}N_7O_2$: C, 69.56; H, 3.54; N, 20.28. Found: C, 69.49; H, 3.60; N, 20.20%.

8-Amino-3-phenylcarbamoyl-7-cyano-5-oxo-1,6-diphenyl-1, 5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine (**10e**): Color: yellow (from ethanol). Yield: 80%. M.p.: 238-240 °C. FT-IR (KBr, ν, cm^{-1}): 3382, 3163, 3109 (NH, NH_2), 3058 (CH, aromatic), 2221(CN) 1705,1643 (C=O), 1600 (C=N), 1527 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.01-8.22 (m, 17H, ArH's), 11.71 (s, br, 1H, NH). Anal. calcd. for $C_{28}H_{18}N_8O_2$: C, 67.46; H, 3.64; N, 22.48. Found: C, 67.39; H, 3.59; N, 22.41%.

8-Amino-3-(2-benzofuroyl)-7-(benzothiazol-2-yl)-1,6-di-phenylpyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**11a**): Color: Red (from ethanol). Yield: 80%. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 3200,3110 (NH_2), 3050 (CH, aromatic), 1631 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.19 (s, br., 2H, NH_2), 6.92-8.05 (m, 19H, ArH's). Anal. calcd. for $C_{36}H_{21}N_7O_3S$: C, 68.45; H, 3.35; N, 15.52; S, 5.08. Found: C, 68.33; H, 3.46; N, 15.40; S, 4.98%.

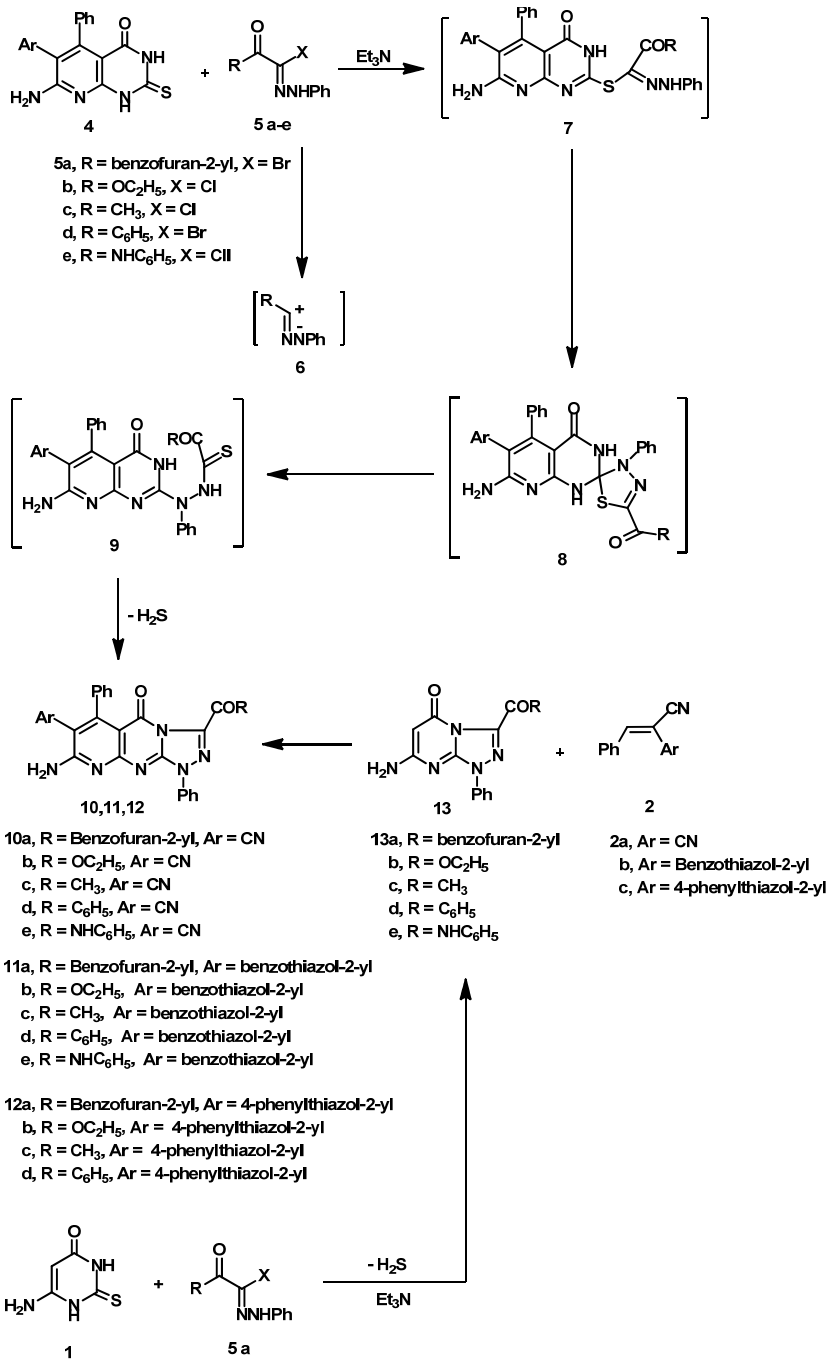
Ethyl 8-amino-7-(benzothiazol-2-yl)-5-oxo-1,6-diphenyl pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-3-carboxylate (**11b**): Color: Orange (from *N,N*-dimethylformamide). Yield: 80%. M.p.: 280-281 °C. FT-IR (KBr, ν, cm^{-1}): 3332, 3224 (NH_2), 3035 (CH, aromatic), 1732, 1635 (CO's). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.20 (t, 3H, *J* = 7.5 Hz, CH_3), 4.20 (q, 2H, *J* = 7.5 Hz, CH_2), 6.76 (br., 2H, NH_2), 7.13-8.96 (m, 14H, ArH's). MS (EI, *m/z* (%)): 561 (M^{+2}, 4.3), 559 (M^+, 3.3), 558 (M^-, 11.5), 486 (24.9), 371 (13.4), 174 (5.7), 134 (10.0, 77 (100.0). Anal. calcd. for $C_{30}H_{21}N_7O_3S$: C, 64.39; H, 3.78; N, 17.52; S, 5.73. Found: C, 64.46; H, 3.70; N, 17.61; S, 5.65%.

8-Amino-3-acetyl-7-(benzothiazol-2-yl)-1,6-diphenylpyrido [2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**11c**): Color: Red (from ethanol). Yield: 83%. M.p.: 180-181 °C. FT-IR (KBr, ν, cm^{-1}): 3330, 3222 (NH_2), 3038 (CH, aromatic), 11682, 1640 (CO's). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 3H, $COCH_3$), 7.12-7.48 (m, 16H, ArH's and NH_2). MS (EI, *m/z* (%)): 529 (M^+, 12.2), 252 (12.2), 240 (6.1), 174 (16.3), 134 (18.4), 57 (100.0). Anal. calcd. for $C_{29}H_{19}N_7O_2S$: C, 65.77; H, 3.62; N, 18.51; S, 6.05. Found: C, 65.69; H, 3.71; N, 18.43; S, 6.12%.

8-Amino-3-benzoyl-7-(benzothiazol-2-yl)-1,6-diphenylpyrido [2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**11d**): Color: Red (from ethanol). Yield: 75%. M.p.: 90-92 °C. FT-IR (KBr, ν, cm^{-1}): 3479, 3394 (NH_2), 3050 (CH, aromatic), 1689 (CO), 1593 (C=N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.22 (s, br., 2H, NH_2), 7.12-8.11 (m, 19H, ArH's). Anal. calcd. for $C_{34}H_{21}N_7O_2S$: C, 69.02; H, 3.58; N, 16.57; S, 5.42. Found: C, 69.11; H, 3.50; N, 16.65; S, 5.50%.

8-Amino-N-phenyl-7-(benzothiazol-2-yl)-5-oxo-1,6-diphenyl pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-3-carboxamide (**11e**): Color: Yellow (from ethanol). Yield: 75%. M.p.: 180-182 °C. FT-IR (KBr, ν, cm^{-1}): 3382, 3159, 3109 (NH, NH_2), 3020 (CH, aromatic), 1647 (CO), 1600 (C=C), 1531 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.45 (s, br., 3H, NH, NH_2), 7.12-8.11 (m, 19H, ArH's). Anal. calcd. for $C_{34}H_{22}N_8O_2S$: C, 67.31; H, 3.66; N, 18.47; S, 5.29. Found: C, 67.21; H, 3.60; N, 18.40; S, 5.20%.

8-Amino-3-(2-benzofuroyl)-7-(4-phenylthiazol-2-yl)-1,6-di-phenylpyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**12a**): Color: Red (from ethanol). Yield: 80%. M.p.: 185-187 °C. FT-IR (KBr, ν, cm^{-1}): 3425, 3363 (NH_2), 3062 (CH, aromatic), 1660 (CO). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.92 (s, br., 2H, NH_2), 7.00-8.18 (m, 21H, ArH's). Anal. calcd. for $C_{38}H_{23}N_7O_3S$: C, 69.39; H, 3.52; N, 14.91; S, 4.88. Found: C, 69.29; H, 3.61; N, 14.78; S, 4.93%.



Scheme 2

Ethyl 8-amino-7-(4-phenylthiazol-2-yl)-5-oxo-1,6-diphenyl pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-3-carboxylate (**12b**): Color: Yellow (from *N,N*-dimethylformamide). Yield: 85%. M.p.: 290-292 °C. FT-IR (KBr, ν, cm^{-1}): 3471, 3394 (NH_2), 3043 (CH, aromatic), 1743, 1697 (C=O), 1600 (C=N), 1546 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.21 (t, 3H, *J* = 7.5 Hz, CH_3), 4.35 (q, 2H, *J*= 7.5 Hz, CH_2), 7.22-8.20 (m, 18H, ArH's and NH_2). Anal. calcd. for $C_{32}H_{23}N_7O_3S$: C, 65.63; H, 3.96; N, 16.74; S, 5.48. Found: C, 65.70; H, 3.88; N, 16.82; S, 5.57%.

8-Amino-3-acetyl-7-(4-phenylthiazol-2-yl)-1,6-diphenyl pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**12c**): Color: Red (from ethanol). Yield: 80%. M.p.: 180-182 °C. FT-IR (KBr, ν, cm^{-1}): 3471, 3394 (NH_2), 3043 (CH, aromatic), 1697 (C=O), 1600 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.10 (s, 3H, $COCH_3$), 4.21 (brs, 2H, NH_2), 7.24-8.02 (m, 16H, ArH's). Anal. calcd. for $C_{31}H_{21}N_7O_2S$: C, 67.01; H, 3.81; N, 17.65; S, 5.77. Found: C, 67.10; H, 3.89; N, 17.57; S, 5.67%.

8-Amino-3-benzoyl-7-(4-phenylthiazol-2-yl)-1,6-diphenyl pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**12d**): Color: Red (from ethanol). Yield: 80%. M.p.: 110-112 °C. FT-IR (KBr, ν, cm^{-1}): 3425, 3386 (NH_2), 3062 (CH, aromatic), 1708 (C=O), 1596 (C=N), 1554 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.88 (s, br., 2H, NH_2), 7.27-8.30 (m, 21H, ArH's and

thiazole H-5). Anal. calcd. for $C_{36}H_{23}N_7O_2S$: C, 70.00; H, 3.75; N, 15.87; S, 5.19. Found: C, 70.10; H, 3.65; N, 15.77; S, 5.27%.

2.2.3. 7-amino-3-(2-benzofuroyl)-1-phenyl-[1,2,4]triazolo [4,3-a]pyrimidin-5(1H)-one (13)

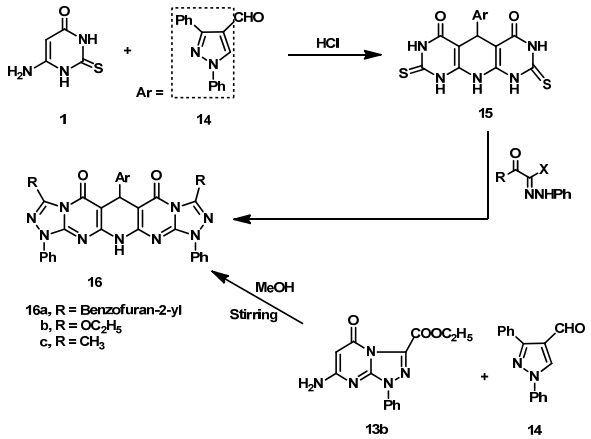
A mixture of compound **1** (5 mmol), the appropriate hydrazonoyl halides **5a** (5 mmol) and triethylamine (5 mmol) in chloroform were heated under reflux for 10 hrs. The excess solvent was evaporated and the residue was triturated with ethanol (10 mL). The solid formed was filtered off and crystallized from ethanol to give compound **13** (Scheme 2). Color: Red (from ethanol). Yield: 80%. M.p.: 150-152 °C. FT-IR (KBr, ν, cm^{-1}): 3421, 3379 (NH_2), 3055 (CH, aromatic), 1631 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.94 (s, 1H, H-6), 6.21 (s, br., 2H, NH_2), 7.39-8.51 (m, 10H, ArH's). Anal. calcd. for $C_{20}H_{13}N_5O_3$: C, 64.69; H, 3.53; N, 18.86. Found: C, 64.60; H, 3.47; N, 18.78%.

2.2.4. Alternative synthesis of compounds 10-12

A mixture of the appropriate **13a-e** 7-amino-1-phenyl-5-oxo-1,2,4-triazolo[4,3-*a*]pyrimidine [26] **13** (5 mmol) and the appropriate of arylidene **2a-c** (5 mmol) in absolute ethanol (10 mL) containing triethylamine was heated under reflux for 3 h. The reaction mixture was concentrated and cooled. The solid obtained was filtered off, washed with ethanol and recrystallized from a proper solvent to give products identical in all aspects (M.p., mixed m.p. and spectra) with the corresponding products obtained by method A (Scheme 2).

2.2.5. 10-(1,3-Diphenyl-1H-pyrazol-4-yl)-2,7-dithioxo-2,3,7,8,9,10-hexahydro-1H,6H-1,3,6,8,9-pentaaza-anthracene-4,5-dione (15)

To a solution of 6-amino thiouracil (**1**), (5 mmol) in methanol (10 mL) and concentrated hydrochloric acid (0.4 mL), compound **14** was added and stirred at room temperature for 4 h, the solid that obtained was collected by filtration and crystallized from *N,N*-dimethylformamide to give compound **15** (Scheme 3). Color: Orange. Yield: 75%. M.p.: >300 °C. FT-IR (KBr,ν, cm^{-1}): 3444, 3321, 3200 (NH), 3058 (CH, aromatic), 1654 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.76 (s, 1H, CH), 7.24-7.82 (m, 11H, ArH's and pyrazole H-5)), 11.95 (s, 2H, 2NH), 14.07 (s, br., 3H, 3NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 21.65, 100.11, 115.21, 122.64, 124.23, 125.85, 127.35, 127.89, 129.42, 136.472, 137.54, 138.29, 145.11, 155.20, 172.98. Anal. calcd. for $C_{24}H_{17}N_7O_2S_2$: C, 57.70; H, 3.43; N, 19.63; S, 12.84. Found: C, 57.62; H, 3.34; N, 19.53; S, 12.93%.



Scheme 3

2.2.6. Synthesis of compounds 16a-c

A mixture of compound **15** (5 mmol), the appropriate hydrazonoyl halides **5a-c** (5 mmol) and triethylamine (5 mmol) in chloroform were heated under reflux for 10 hrs. The excess solvent was evaporated and the residue was triturated with ethanol (10 mL). The solid formed was filtered off and crystallized from a proper solvent to give **16a-c**, respectively (Scheme 3).

3,7-Bis-(benzofuran-2-carbonyl)-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,9-diphenyl-5,11-dihydro-1H,9H-1,2,3a,6a,8,9,10,11,12-nonaaza-dicyclopenta[b,i]anthracene-4,6-dione (**16a**): Color: Red (from ethanol). Yield: 75%. M.p.: 202-204 °C. FT-IR (KBr, ν, cm^{-1}): 3328 (NH), 3062 (CH, aromatic), 1662 (CO). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.45 (s, 1H, CH), 7.01-8.23 (m, 31H, ArH's), 11.88 (s, br., 1H, NH). Anal. calcd. for $C_{56}H_{33}N_{11}O_6$: C, 70.36; H, 3.48; N, 16.12. Found: C, 70.26; H, 3.39; N, 16.03%.

5-(1,3-Diphenyl-1H-pyrazol-4-yl)-4,6-dioxo-1,9-diphenyl-5,6,9,11-tetrahydro-1H,4H-1,2,3a,6a,8,9,10,11,12-nonaaza-dicyclopenta[b,i]anthracene-3,7-dicarboxylic acid diethyl ester (**16b**): Color: Orange (from ethanol). Yield: 80%. M.p.: 180-182 °C. FT-IR (KBr, ν, cm^{-1}): 3328 (NH), 3062 (CH, aromatic), 1735, 1674 (CO's), 1647 (C=N), 1600 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.07 (t, 6H, *J* = 7*Hz*, $2CH_3$), 4.40 (q, 4H, *J* = 7*Hz*, $2CH_2$), 6.20 (s, 1H, CH-9), 6.88-8.08 (m, 21H, ArH's), 11.27 (s, 1H, NH). Anal. calcd. for $C_{44}H_{33}N_{11}O_6$: C, 65.10; H, 4.10; N, 18.98. Found: C, 65.19; H, 4.00; N, 18.89%.

3,7-Diacetyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,9-diphenyl-5,11-dihydro-1H,9H-1,2,3a,6a,8,9,10,11,12-nonaaza-dicyclo penta[b,i]anthracene-4,6-dione (**16c**): Color: Orange (from ethanol). Yield: 83%. M.p.: 268-270 °C. FT-IR (KBr, ν, cm^{-1}): 3394 (NH), 3058 (CH, aromatic), 1631 (CO). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.72 (s, 6H, $2CH_3CO$), 5.12 (s, 1H, CH), 7.12-8.11 (m, 21H, ArH's), 11.87 (s, br., 1H, NH). Anal. calcd. for $C_{42}H_{29}N_{11}O_4$: C, 67.10; H, 3.89; N, 20.50. Found: C, 67.19; H, 3.80; N, 20.42%.

2.2.7. Synthesis of compound 18a-c

A mixture of compound **17** [27] (5 mmol), the appropriate hydrazonoyl halides **5a-c** (5 mmol) and triethylamine (5 mmol) in chloroform were heated under reflux for 10 hrs. The excess solvent was evaporated and the residue was triturated with ethanol (10 mL). The solid formed was filtered off and crystallized from a proper solvent to give compound **18a-c**, respectively (Scheme 4).

3,7-Bis-(benzofuran-2-carbonyl)-1,9-diphenyl-5,11-dihydro-1H,9H-1,2,3a,6a,8,9,10,11,12-nonaaza-dicyclopenta[b,i]anthrax-cene-4,6-dione (**18a**): Color: White (from ethanol). Yield: 70%. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 3120 (NH) 1724, 1681(C=O), 1604 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.66 (s, 2H, CH_2), 7.17-8.12 (m, 20H, ArH's), 11.87 (s, br., 1H, NH). Anal. calcd. for $C_{41}H_{23}N_9O_6$: C, 66.76; H, 3.14; N, 17.09. Found: C, 66.68; H, 3.24; N, 17.12%.

4,6-Dioxo-1,9-diphenyl-5,6,9,11-tetrahydro-1H,4H-1,2,3a,6a, 8,9,10,11,12-nonaaza-dicyclopenta[b,i]-anthracene-3,7-dicar-boxylic acid diethyl ester (**18b**): Color: Yellow (from ethanol). Yield: 70%. M.p.: 138-140 °C. FT-IR (KBr, ν, cm^{-1}): 3386 (NH), 1747 (C=O ester), 1681 (C=O), 1600 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.14 (t, 6H, *J* = 7 Hz, $2CH_3$), 3.56 (s, 2H, CH_2), 4.13 (q, 4H, *J* = 7 Hz, $2CH_2$), 6.99-7.35 (m, 10H, ArH's), 10.8 (s, 1H, NH). Anal. calcd. for $C_{29}H_{23}N_9O_6$: C, 58.68; H, 3.91; N, 21.24. Found: C, 58.78; H, 4.00; N, 21.31%.

3,7-Diacetyl-1,9-diphenyl-5,11-dihydro-1H,9H-1,2,3a,6a,8,9, 10,11,12-nonaaza-dicyclopenta[b,i]anthracene-4,6-dione (**18c**): Color: White (from ethanol). Yield: 68%. M.p.: 200-202 °C. FT-IR (KBr, ν, cm^{-1}): 3120 (NH), 1724, 1681(C=O), 1604 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 6H, $2CH_3$), 3.65 (s, 2H, CH_2), 7.02-7.54 (m, 10H, ArH's), 12.08 (s, 1H, NH).

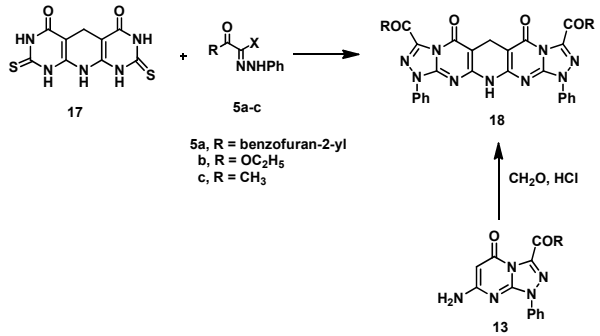
Table 1. The antimicrobial activity of the newly synthesized compounds *.

Sample No	Microorganism / Mean of zone diameter, nearest whole mm							
	Gram-positive bacteria		Gram-negative bacteria		Fungi			
	Bacillus Subtilis (ATCC 6635)		Escherichia coli (ATCC 25922)		Candida Albicans (ATCC 10231)		Aspergillus Fumigatus	
	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	0.5 mg/mL
4a	11 (L)	7 (L)	-	-	-	-	-	-
4b	13 (L)	7 (L)	-	-	13 (I)	10 (I)	12 (I)	8 (I)
4c	10 (L)	8 (L)	-	-	-	-	-	-
10b	-	-	12 (I)	7 (I)	-	-	11 (L)	7 (L)
10c	-	-	-	-	-	-	-	-
11a	-	-	14 (I)	11 (I)	-	-	-	-
11c	-	-	-	-	-	-	-	-
12a	11 (L)	8 (L)	-	-	-	-	-	-
12c	-	-	-	-	-	-	-	-
18a	-	-	-	-	-	-	-	-
18b	10 (L)	7 (L)	-	-	11 (L)	7 (L)	-	-
Control #	35	38	38	27	35	35	37	26

* Identified on the basis of routine culture, morphological and microscopical characteristics: - = 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).

Chloramphencol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria and Cycloheximide in the case of fungi.

Anal. calcd. for $C_{27}H_{19}N_9O_4$: C, 60.79; H, 3.59; N, 23.63. Found: C, 60.70; H, 3.50; N, 23.54%.



Scheme 4

2.3. Antimicrobial activity

The tested compounds were dissolved in DMF and prepared in two concentrations; 50 and 100 mg/mL and then 10 µL of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 0.5 and 1.0 mg/mL, respectively. Uniform size filter paper disks (6 mm in diameter) were impregnated by volume (10 µL) from the specific concentration of dissolved compounds and carefully placed on inoculated agar surface. After incubation for 36 hrs at 27 °C in the case of bacteria and for 48 hrs at 24 °C in the case of fungi, inhibition of the organisms which evidenced by clear zone surround each disk was measured and used to calculate mean of inhibition zone [28].

3. Results and discussion

3.1. Synthesis

Condensation of 6-aminothiouracil (**1**) with the appropriate amount of benzylidene malononitril (**2a**), 2-(benzo[*d*]thiazol-2-yl)-3-phenylacrylonitrile (**2b**) and 3-phenyl-2-(4-phenyl-thiazol-2-yl)acrylonitrile (**2c**) in ethanol containing triethyl-amine under reflux gave 7-amino-6-substituted 5-phenyl-2,3-dihydro-2-thioxo-pyrido[2,3-*d*] pyrimidin-4(1*H*)-one, **4a-c**, respectively (Scheme 1). Structures **4a-c** were confirmed by elemental analyses, spectral data and chemical transformation.

Thus, treatment of pyrido[2,3-*d*] pyrimidine derivative **4a** with *C*-benzofuran-2oyl-*N*-phenylhydrazonoyl bromide **5a** in boiling chloroform containing triethylamine afforded 8-Amino-3-(benzofuran-2-yl-carbonyl)-7-cyano-5-oxo-1,6-diphenyl-1,5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine (**10a**). Structure of compound **10a** was elucidated via elemental analysis, spectral data and alternative synthesis. Thus, reaction of compound **2a** with 7-amino-3-(1-benzofuran-2-yl-carbonyl)-1-phenyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**13a**), which was prepared via reaction of compound **1** with compound **5a**, in boiling ethanolic triethylamine gave product identical in all aspects (M.p., mixed m.p., and spectra) with compound **10a**.

The mechanism outlined in Scheme 2 seems to be the most plausible pathway for the formation of compound **10a** from the reaction of compound **4a** with compound **5a** or nitrile imine **6a**, which was prepared in situ by treatment of compound **5a** with triethylamine, the reaction involves the initial formation of thiohydrazonate **7a**, which undergoes intermolecular cyclization as soon as it is formed to yield the intermediate **8a** or via 1,3-dipolar cycloaddition of nitrilimine **6a** to C=S double bond of **4a** to give final product compound **10a** via elimination of hydrogen sulphide.

Analogously, the appropriate hydrazonoyl halides **5b-e** reacted with the appropriate **4a-c** in boiling chloroform in presence of catalytical amount of triethylamine gave compound **10b-e**, **11a-e** and **12a-d**, respectively (Scheme 2).

Also, reaction of compound **1** with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**14**) in methanol containing few drops of hydrochloric acid led to the formation of 10-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,7-dithioxo-2,3,7,8,9,10-hexa-hydro-1*H*,6*H*-1,3,6,8,9-pentaaza-anthracene-4,5-dione (**15**) (Scheme 4). Structure compound **15** was confirmed by spectral data, elemental analyses and chemical transformation. Thus, compound **15** react with hydrazonoyl halides **5a-c** in boiling chloroform to give **16a-c**, respectively. ^{1}H NMR spectrum of compound **16b** showed signals at 1.07 (t, 3H, *J* = 7 Hz, CH_3), 4.40 (q, 2H, *J* = 7 Hz CH_2), 6.02 (s, 1H, CH-9), 6.88-8.08 (m, 10H, ArH's), 11.27 (s, 1H, NH) ppm.

Moreover, reaction of 2,8-dithioxo-2,3,7,8,9,10-hexahydro-pyrido[2,3-d:6,5-d']dipyrimidine-4,6(1*H*,5*H*)-dione (**17**) [29] with the appropriate hydrazonoyl halides **5a-c** were carried out in chloroform under reflux for along time gave compound **18a-c** (Scheme 4). Structures **18** were inferred from their spectral data, elemental analyses and alternative synthesis. Thus ^{1}H NMR spectrum of **18b** showed signals at δ = 1.14 (t, 6H, *J* = 7 Hz, $2CH_3$), 3.56 (s, 2H, CH_2), 4.13 (q, 4H, *J* = 7 Hz, $2CH_2$), 6.99-7.35 (m, 10H, ArH's), 10.8 (s, 1H, NH). Its IR spectrum revealed bands at 3386 (NH) 1747 (CO ester), 1681 (CO), 1600 (C=C). Thus, compound **13b** reacted with formaldehyde in presence of hydrochloric acid gave product identical in all aspect (M.p., mixed m.p., and spectra) with compound **18b.**

3.2. Antimicrobial activity

The tested microorganisms were Gram-positive bacteria: *Staphylococcus Aureus* (ATCC 25923) and *Bacillus Subtilis* (ATCC 6635), Gram-negative bacteria: *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922), Fungus: *Candida Albicans* (ATCC 10231) and *Aspergillus fumigatus*.

In general, (for high and low concentrations) compounds **4a-c**, **12a** and **18b** were capable low inhibition against Gram-positive bacteria *Bacillus Subtilis* and compounds **10b** and **11a** were capable intermediate inhibition against Gram-negative bacteria *Escherichia coli* whereas compound **4a** show intermediate inhibition against yeast and fungi (Table 1). *Staphylococcus Aureus* (ATCC 25923) and *Salmonella typhimurium* (ATCC 14028) are no effect for all synthesized compounds.

4. Conclusion

The present work describes the study of reactions of hydrazonoyl halides towards some pyridodipyrimidinethione derivatives to give pyridotriazolopyrimidines derivatives in a good yield with some biological activity.

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