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Pyridazine and its related compounds: Part 38. Pyrimido[1,2-b]pyridazinone, synthesis and some reactions

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ABSTRACT

A new method of generating the fused heterocyclic system with bridge head nitrogen pyrimido[1,2-b]pyridazinone, from 3-amino-4,5,6-triphenylpyridazine and malonic acid in presence of phosphoryl chloride is described. The structures of the synthesized compounds were confirmed by their infrared, mass spectrum, ^{1}H NMR and elemental analyses. The antimicrobial activity of the compounds obtained was examined against some selected microorganisms.

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1. Introduction

The pyridazines and pyrimidines are important and significant classes of heterocyclic compounds [1-3]. A number of their derivatives have found diverse uses in synthetic, analytical, medicinal, pharmaceutical, agrochemical, and photographic chemistry. Sometimes the fusion of heterocyclic nuclei enhances the pharmacological activities much more than its parent nucleus. Hence, it was thought that the incorporation of the latter heterocyclic moieties into a pyridazine system might modify their biological activities.

The present investigation is in continuation of our previous work [4-6] on the synthesis and biological activity of other pyridazine derivatives. In the accompanying paper [5], we have described the preparation of 3-amino-4,5,6-triphenyl pyridazine a useful starting material for the preparation of 7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-dione, **1**. In this paper, we wish to show that compound **1** is also useful building blocks for the synthesis of a wide variety of pyrimidopyridazine derivatives and to test their anti-microbial activity.

2. Experimental

2.1. Instrumentation

Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were carried out in the Micro Analytical Laboratory of the Faculty of Science, Cairo University, Egypt. The IR spectra of compounds were recorded on a Nicolet 6700 FT-IR (Thermo Scientific) as potassium bromide pellets and frequencies are reported in cm^{-1}. The mass spectra were recorded on a GC-MS model Shimadzu Qp-2010 plus EI 70 eV. The ^{1}H NMR spectra were recorded on a Varian Gemini-300 MHz NMR spectrometer and chemical shifts δ are in ppm relative to internal TMS. Reactions were routinely followed by thin layer chromatography (TLC) on silica gel; F_{254} aluminum sheets (Merck). The spots were detected by UV irradiation at 254-365 nm.

2.2. Synthesis

2.2.1. Synthesis of 7,8,9-triphenyl-2H-pyrimido[1,2-b] pyridazine-2,4(3H)-dione (1)

A mixture of 3-amino-4,5,6-triphenylpyridazine [5] (0.5 g, 1.55 mmol), malonic acid (0.16 g, 1.55 mmol) and phosphoryl chloride (10 mL) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and poured into ice cooled water (200 mL).

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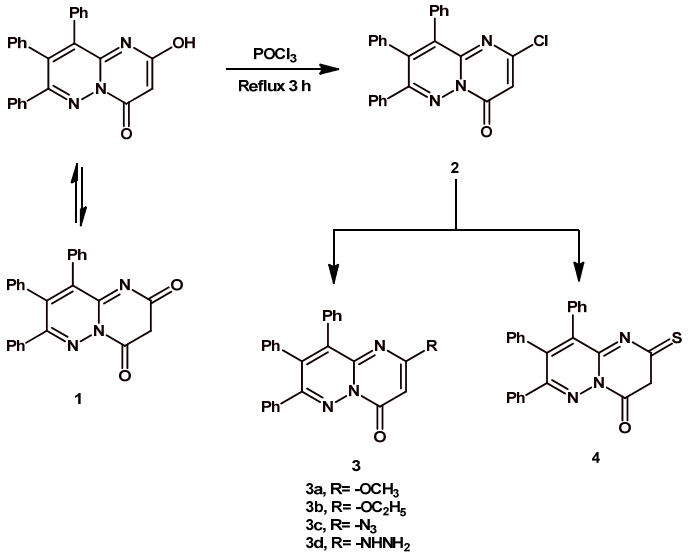


Scheme 1

The solid product was filtered off, washed with water, dried and recrystallized from ethanol (Scheme 1). Color: Yellow. Yield: 72.70%. M.p.: 188-190 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH Arom.), 2923 (CH Aliph.), 1703 (C=O), 1636 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.99 (s, 2H, CH_2), 6.78-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)): 391 (M^+, 72.07), 363 (11.24), 349 (10.60), 335 (5.41), 321 (16.82), 314 (4.59), 288 (3.35), 213 (3.30), 178 (25.40), 103 (4.85), 69 (100). Anal. calcd. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.74. Found: C, 76.50; H, 4.4.20; N, 10.60%.

2.2.2. Synthesis of 2-chloro-7,8,9-triphenyl-4H-pyrimido [1,2-b]pyridazin-4-one (2)

A mixture of 7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*] pyridazine-2,4(3*H*)-dione (**1**) (0.5 g, 1.28 mmol) and phosphoryl chloride (10 mL) was refluxed for 3 h. The reaction mixture was cooled, poured into ice cold water (200 mL), and then the solid product formed was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **2** (Scheme 1). Color: Brown. Yield: 84.13 %. M.p.: 226-228 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (C-H, Arom.), 1703 (C=O), 1638 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.65 (s, 1H, CH, pyrimidine ring), 6.78-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)): 412 (M^++2, 3.50), 410 (M^+, 51.22), 408 (100), 374 (5.13), 369 (5.29), 349 (5.54), 333 (8.63), 307 (7.82), 267 (9.93), 178 (11.32), 103 (5.46), 76 (9.69), 60 (11.07). Anal. calcd. for $C_{25}H_{16}ClN_3O$: C, 73.26; H, 3.93; N, 10.25. Found: C, 73.59; H, 3.78; N, 10.52%.

2.2.3. Synthesis of 2-methoxy-7,8,9-triphenyl-4H-pyrimido [1,2-b]pyridazin-4-one (3a)

Compound **2** (0.5 g, 1.22 mmol) was added to a solution of sodium methoxide (0.1 g of Na in 10 mL of pure methanol). The reaction mixture was refluxed for 3 h. The solvent was concentrated, and then the solid product was filtered off, dried, and recrystallized from ethanol to give compound **3a** (Scheme 1). Color: Brown crystals. Yield: 74.75%. M.p.: 146-148 °C. FT-IR (KBr, ν, cm^{-1}): 3056 (C-H, Arom.), 2927 (C–H, Aliph.), 1705 (C=O), 1645 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.66 (s, 3H, CH_3), 5.87 (s, 1H, CH, pyrimidine ring), 6.89-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)):405 (M^+, 96.55), 390 (72.41), 376 (75.86), 349 (81.61), 334 (59.77), 200 (100), 71 (75.86), 57 (31.03). Anal. calcd. for $C_{26}H_{19}N_3O_2$: C, 77.02; H, 4.72; N, 10.36. Found: C, 77.39; H, 4.53; N, 10.62%.

2.2.4. Synthesis of 2-ethoxy-7,8,9-triphenyl-4H-pyrimido [1,2-b]pyridazin-4-one (3b)

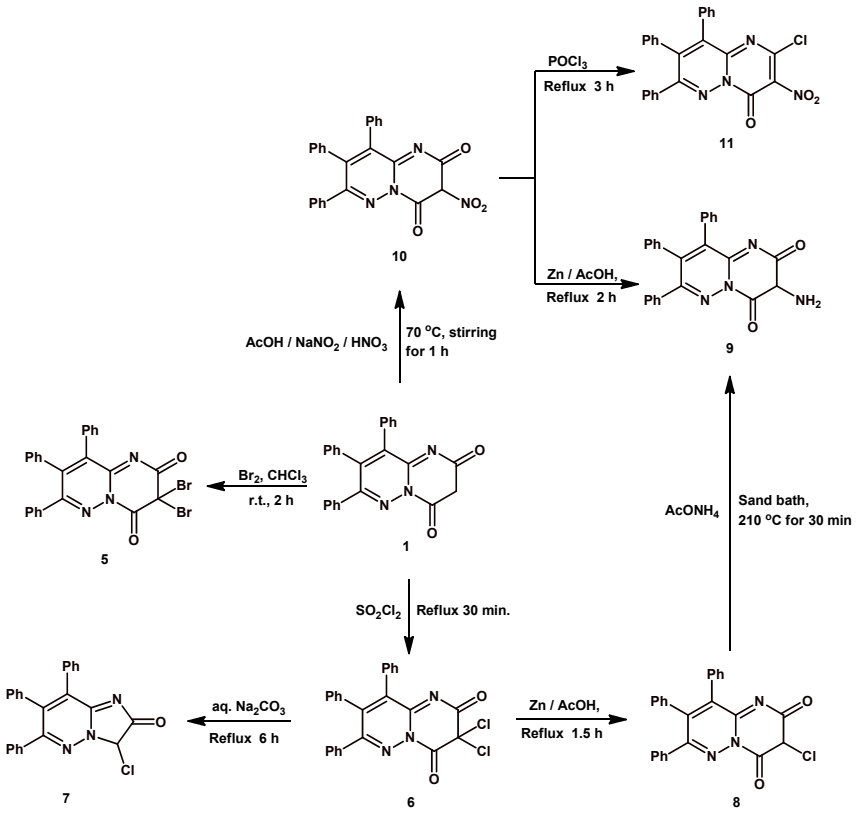
Compound **2** (0.5 g, 1.22 mmol) was added to a solution of sodium ethoxide (0.1 g of Na in 10 mL of absolute ethanol). The reaction mixture was refluxed for 3 h. The solvent was concentrated; and then the solid product was filtered off, dried, and recrystallized from ethanol to give compound **3b** (Scheme 1). Color: Brown. Yield: 74.26 %. M.p.: 200-205 °C. FT-IR (KBr, ν, cm^{-1}): 3058 (CH, Arom.), 2975, 2924 (CH, Aliph.), 1695 (C=O), 1643 (C=N), 1234 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.14 (t, 3H, CH_2CH_3), 4.05 (q, 2H, CH_2CH_3), 5.67 (s, 1H, CH, pyrimidine ring), 6.94-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)):419 (M^+, 14.45), 404 (7.00), 390 (23.58), 322 (100), 307 (4.01), 178 (18.86), 138 (4.78), 77 (43.56). Anal. calcd. for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.67; H, 4.88; N, 10.25%.

2.2.5. Synthesis of 2-azido-7,8,9-triphenyl-4H-pyrimido[1,2-b]pyridazin-4-one (3c)

A solution of compound **2** (0.5 g, 1.22 mmol), and sodium azide (0.24 g, 3.66 mmol) in dimethylformamide (10 mL) was heated at 100 °C for 3 h. The reaction mixture was cooled, poured into ice cold water (100 mL). The solid product was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **3c** (Scheme 1). Color: Brown. Yield: 76.77 %. M.p.: 190-192 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 2209 (N_3), 1652 (C=O), 1612 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.88 (s, 1H, CH, pyrimidine ring), 6.89-7.37 (m, 15H, 3Ph). MS (EI, *m/z* (%)): 416 (M^+, 3.20), 388 (33.45), 374 (5.81), 322 (100), 237 (7.83), 178 (9.25), 77 (17.08). Anal. calcd. for $C_{25}H_{16}N_6O$: C, 72.10; H, 3.87; N, 20.18. Found: C, 72.48; H, 3.99; N, 20.01%.

2.2.6. Synthesis of 2-hydrazinyl-7,8,9-triphenyl-4H-pyrimido[1,2-b]pyridazin-4-one (3d)

A solution of compound **2** (0.5 g, 1.22 mmol), and hydrazine hydrate (0.1 mL, 1.22 mmol) in ethanol (10 mL) was heated under reflux for 3 h.



Scheme 2

The solvent was evaporated, and the residue was triturated with cold water. The solid product formed was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **3d** (Scheme 1). Color: Brown. Yield: 68.69 %. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3313, 3204 (NH, NH_2), 3058 (C–H, Arom.), 1691 (C=O). MS (EI, *m/z* (%)):405 (M^+, 7.26), 388 (6.15), 322 (100), 306 (5.49), 251 (4.10), 178 (10.99), 98 (3.26), 77 (17.97). Anal. calcd. for $C_{25}H_{19}N_5O$: C, 74.06; H, 4.72; N, 17.27. Found: C, 74.38; H, 4.83; N, 17.54%.

2.2.7. Synthesis of 7,8,9-triphenyl-2-thioxo-2H-pyrimido [1,2-b]pyridazin-4(3H)-one (4)

A solution of compound **2** (0.5 g, 1.22 mmol), and thiourea (0.5 g) in ethanol (10 mL) was heated under reflux for 2 h. The solvent was evaporated, and the residue was dissolved in sodium hydroxide (10 %). The reaction mixture was heated under reflux for 30 min., and filtered on hot. The filtrate was cooled, neutralized with hydrochloric acid; the formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **4** (Scheme 1). Color: Brown. Yield: 68.4 %. M.p.: 212-213 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 2968, 2926 (CH, Aliph.), 1705 (C=O), 1638 (C=N), 1236 (C=S). MS (EI, *m/z* (%)):407 (M^+, 44.59), 377 (36.31), 349 (39.49), 336 (51.59), 320 (33.12), 307 (38.22), 268 (42.04), 229 (35.03), 178 (35.03), 139 (44.59), 100 (7.01), 86 (45.22), 64 (100). Anal. calcd. for $C_{25}H_{17}N_3OS$: C, 73.69; H, 4.21; N, 10.31. Found: C, 73.98; H, 4.06; N, 10.53%.

2.2.8. Synthesis of 3,3-dibromo-7,8,9-triphenyl-2H-pyrimido [1,2-b]pyridazine-2,4(3H)-dione (5)

To a solution of compound **1** (0.5 g, 1.28 mmol) in chloroform (10 mL), bromine (2.56 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was triturated with water. The solid product was filtered off, washed with water, dried, and recrystallized from methanol to give compound **5** (Scheme 2). Color: Brown. Yield: 68.41 %. M.p.: 118-120 °C. FT-IR (KBr, ν, cm^{-1}): 3056 (CH, Arom.), 1710 (C=O), 1637 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.96-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)): 549 (M^+, 30.60), 520 (21.35), 508 (34.52), 469 (23.13), 388 (23.13), 377 (19.57), 372 (22.06), 357 (20.64), 193 (6.76), 172 (24.20), 160 (25.27), 80 (100). Anal. calcd. for $C_{25}H_{15}Br_2N_3O_2$: C, 54.67; H, 2.75; N, 7.65. Found: C, 55.03; H, 2.86; N, 7.51%.

2.2.9. Synthesis of 3,3-dichloro-7,8,9-triphenyl-2H-pyrimido [1,2-b]pyridazine-2,4(3H)-dione (6)

A solution of compound **1** (0.5 g, 1.28 mmol) in sulfuryl chloride (10 mL) was refluxed for 30 min. The reaction mixture was cooled, poured into ice cold water (100 mL), and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **6** (Scheme 2). Color: Yellow. Yield: 73.13 %. M.p.: 119-120 °C. FT-IR (KBr, ν, cm^{-1}): 3056 (CH, Arom.), 1713 (C=O), 1643 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.23-7.62 (m, 15H, 3Ph). MS (EI, *m/z* (%)):460 (M^+, 62.86), 417 (77.14), 384 (64.76), 377 (57.14), 284 (72.38), 230 (64.76), 176 (100), 154 (15.24), 126 (33.33), 83 (66.67). Anal. calcd. for $C_{25}H_{15}Cl_2N_3O_2$: C, 65.23; H, 3.28; N, 9.13. Found: C, 65.51; H, 3.18; N, 8.99%.

2.2.10. Synthesis of 3-chloro-6,7,8-triphenylimidazo[1,2-b] pyridazin-2(3H)-one (7)

A mixture of compound **6** (0.5 g, 1.09 mmol) in aq. sodium carbonate solution was refluxed for 6 h. After cooling, the

reaction mixture was filtered off. The residue was triturated with water, filtered off, dried, and recrystallized from ethanol to give compound **7** (Scheme 2). Color: Brown. Yield: 53.23%. M.p.: 215-217 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 1704 (C=O), 1632 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.82 (s, 1H, CH, imidazol ring), 6.89-7.28 (m, 15H, 3Ph). MS (EI, *m/z* (%)):400 (M^+ + 2, 0.02), 398 (M^+, 0.15), 321 (2.10), 307 (2.37), 294 (2.11), 277 (100), 206 (0.30), 192 (1.44), 178 (10.14), 117 (27.40), 103 (1.37), 91 (1.93), 77 (40.94). Anal. calcd. for $C_{24}H_{16}ClN_3O$: C, 72.45; H, 4.05; N, 10.56. Found: C, 72.78; H, 4.17; N, 10.34%.

2.2.11. Synthesis of 3-chloro-7,8,9-triphenyl-2H-pyrimido [1,2-b]pyridazine-2,4(3H)-dione (8)

A solution of compound **6** (0.5 g, 1.09 mmol) in glacial acetic acid (10 mL) in presence of zinc dust was refluxed for 1.5 h, then filtered on hot. The filtrate was cooled, poured into water (100 mL), and the precipitate was filtered off, washed with water, dried, and recrystallized from acetone to give compound **8** (Scheme 2). Color: Colorless. Yield: 69.17 %. M.p.: 160-162 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 1704 (C=O), 1632 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.02 (s, 1H, CH, pyrimidine ring), 7.23-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)):427.5 (M^+ +2, 1.02), 425.5 (M^+, 76.29), 409 (86.60), 185 (100). Anal. calcd. for $C_{25}H_{16}ClN_3O_2$: C, 70.51; H, 3.79; N, 9.87. Found: C, 70.23; H, 3.85; N, 10.08%.

2.2.12. Synthesis of 3-amino-7,8,9-triphenyl-2H-pyrimido [1,2-b]pyridazine-2,4(3H)-dione (9)

Method A: A mixture of compound **8** (0.5 g, 1.17 mmol) and excess of ammonium acetate (3.0 g) was heated in a sand bath at 210 °C for 30 min. After cooling, the solid product was washed with water, filtered off, dried and recrystallized from acetone to give compound **9** (Scheme 2). Color: Pale brown. Yield: 58.70%. M.p.: 128-130 °C. FT-IR (KBr, ν, cm^{-1}): 3326, 3188 (NH_2), 3058, 3031 (CH, Arom.), 1751, 1681 (C=O), 1599 (C=N). MS (EI, *m/z* (%)): 406 (M^+, 0.01), 389 (0.23), 378 (0.07), 335 (0.42), 307 (0.67), 281 (1.02), 277 (100), 267 (2.15), 228 (1.10), 214 (0.32), 206 (1.04), 200 (2.39), 192 (1.10), 178 (1.19), 139 (2.23), 125 (3.61), 99 (0.03), 71 (0.93). Anal. calcd. for $C_{25}H_{18}N_4O_2$: C, 73.88; H, 4.46; N, 13.78. Found: C, 74.17; H, 4.38; N, 13.91%.

Method B: A solution of compound **10** (0.5 g, 1.15 mmol) in glacial acetic acid (10 mL) in presence of zinc dust was refluxed for 2 h, then filtered on hot. The filtrate was cooled and poured into water (100 mL). The precipitate was filtered off, washed with water, dried, and recrystallized to give compound **9**. Yield: 0.26 g, 55.79 %.

2.2.13. Synthesis of 3-Nitro-7,8,9-triphenyl-2H-pyrimido [1,2-b]pyridazine-2,4-(3H)-dione (10)

A solution of compound **1** (0.5 g, 1.28 mmol) in glacial acetic acid (5 mL) was warmed up to 70 °C with stirring reacted with a mixture of $NaNO_2$ (0.18 g, 2.56 mmol), then with concentrated nitric acid (1 mL). The reaction mixture was stirring for h. The solid product was filtered off, washed with water, dried and recrystallized from ethanol to give compound **10** (Scheme 2). Color: Yellow. Yield: 66.43%. M.p.: 110-111 °C. FT-IR (KBr, ν, cm^{-1}): 3431 (OH), 3057 (CH, Arom.), 1721 (C=O), 1645 (C=N), 1521 (NO_2, Asym.), 1345 (NO_2, Sym.). MS (EI, *m/z* (%)):436 (M^+, 14.91), 419 (16.26), 393 (14.63), 355 (14.09), 333 (14.91), 307 (14.63), 230 (14.09), 206 (17.62), 155 (19.24), 80 (100). Anal. calcd. for $C_{25}H_{16}N_4O_4$: C, 68.80; H, 3.70; N, 12.84. Found: C, 68.55; H, 3.87; N, 13.09%.

2.2.14. Synthesis of 2-chloro-3-nitro-7,8,9-triphenyl-4H-pyrimido[1,2-b]pyridazin-4-one (11)

A mixture of compound **10** (0.5 g, 1.15 mmol) and phosphoryl chloride (10 mL) was refluxed for 3 h. The reaction mixture was cooled, and poured into ice water (200 mL). The solid product was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **11** (Scheme 2). Color: Brown. Yield: 69.10%. M.p.: 152-154 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 1718 (C=O), 1640 (C=N), 1524 (NO_2, Asym.), 1345 (NO_2, Sym.). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.94-7.66 (m, 15H, 3Ph). MS (EI, *m/z* (%)):455 (M^+, 0.54), 409 (0.33), 393 (1.95), 378 (0.33), 281 (0.87), 277 (1.63), 267 (1.41), 249 (0.43), 206 (2.28), 188 (0.54), 178 (5.85), 174 (0.87), 77(72.48), 62 (6.50), 56 (100). Anal. calcd. for $C_{25}H_{15}ClN_4O_3$: C, 66.01; H, 3.32; N, 12.32. Found: C, 66.27; H, 3.46; N, 12.09%.

2.2.15. Synthesis of 3-(1-hydroxyethylidene)-7,8,9-triphenyl-2H-pyrimido[1,2-b]pyridazine-2,4(3H)-dione (12)

A solution of compound **1** (0.5 g, 1.28 mmol) in glacial acetic acid (10 mL) in presence of an excess polyphosphoric (1.0 g) acid was refluxed for 2 h. The reaction mixture was cooled, poured into ice cold water (200 mL), and then the solid product formed was filtered off, washed with water, dried, and recrystallized from acetone to give compound **12** (Scheme 3). Color: Yellow. Yield: 70.43%. M.p.: 214-215 °C. FT-IR (KBr, ν, cm^{-1}): 3056 (CH, Arom.), 2921, 2851 (CH, Aliph.), 1713 (C=O), 1647 (C=N). MS (EI, *m/z* (%)):433 (M^+, 70.87), 415 (61.71), 390 (58.25), 348 (61.17), 326 (100), 319 (76.70), 307 (73.79), 279 (53.40), 152 (52.43), 126 (64.08), 109 (89.32), 83 (18.45), 79 (83.50), 76 (67.96). Anal. calcd. for $C_{27}H_{19}N_3O_3$: C, 74.81; H, 4.42; N, 9.69. Found: C, 75.13; H, 4.58; N, 9.87%.

2.2.16. Synthesis of 3-(1-hydroxy-3-phenylallylidene)-7,8,9-triphenyl-2H-pyrimido[1,2-b]pyridazine-2,4(3H)-dione (13)

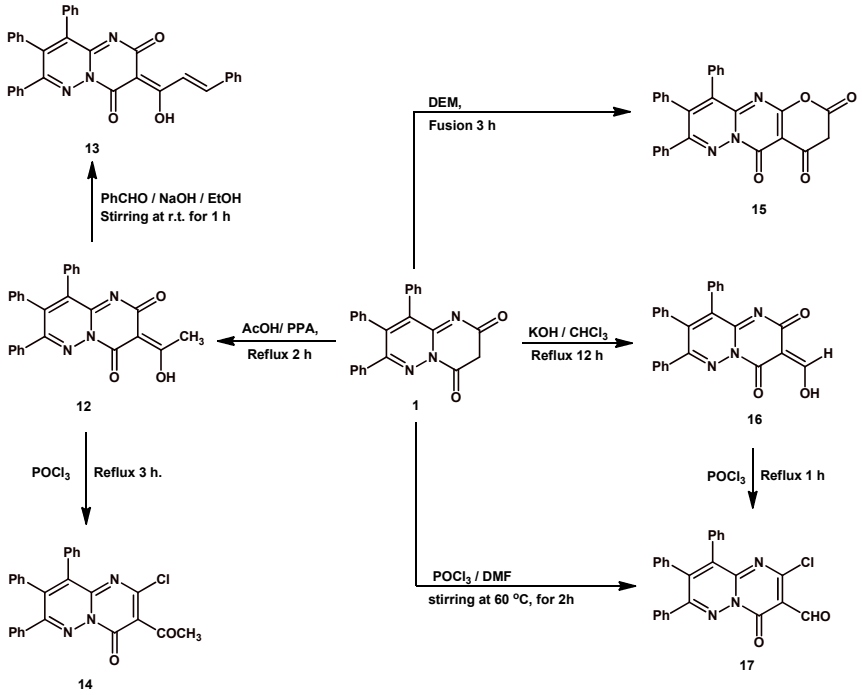
A solution of compound **12** (0.5 g, 1.15 mmol) and benzaldehyde (0.12 mL, 1.15 mmol) in ethanol (10 mL) in presence of sodium hydroxide (0.1 g) was stirred at room temperature for 1 h. The solid product formed was collected, washed with water, dried, and recrystallized from ethanol to give compound **13** (Scheme 3). Color: Yellow. Yield: 68.11%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3372 (OH), 3057, 3028 (CH, Arom.), 1695 (C=O), 1645 (C=N). MS (EI, *m/z* (%)):521 (M^+, 6.45), 504 (0.95), 444 (2.50), 427 (3.68), 416 (7.77), 349 (13.68), 334 (33.44), 186 (12.63), 178 (20.22), 103 (100), 76 (37.66). Anal. calcd. for $C_{34}H_{23}N_3O_3$: C, 78.30; H, 4.44; N, 8.06. Found: C, 78.51; H, 4.59; N, 8.26%.

2.2.17. Synthesis of 3-acetyl-2-chloro-7,8,9-triphenyl-4H-pyrimido[1,2-b]pyridazin-4-one (14)

A mixture of compound **12** (0.5 g, 1.15 mmol) and phosphoryl chloride (10 mL) was refluxed for 3 h. The reaction mixture was cooled, and poured into ice water (200 mL). The solid product was filtered off, washed with water, dried, and recrystallized from ethanol to give compound **14** (Scheme 3). Color: Reddish brown. Yield: 65.22%. M.p.: 175-177 °C. FT-IR (KBr, ν, cm^{-1}): 3058 (CH, Arom.), 2923, 2853 (CH, Aliph.), 1717 (C=O), 1619 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.09 (s, 3H, CH_3), 6.99-7.63 (m, 15H, 3Ph). MS (EI, *m/z* (%)):454 (M^+ + 2, 0.34), 452 (M^+, 0.38), 437 (4.81), 409 (33.37), 408 (100), 375 (0.63), 349 (23.65), 281 (8.56), 274 (2.79), 178 (6.63), 171 (2.55), 103 (22.60), 77 (23.94). Anal. calcd. for $C_{27}H_{18}ClN_3O_2$: C, 71.76; H, 4.01; N, 9.30. Found: C, 71.98; H, 4.12; N, 9.48%.

2.2.18. Synthesis of 2,3,4-triphenylpyrano[2',3':4,5] pyrimido[1,2-b]pyridazine-7,9,10(8H)-trione (15)

A mixture of compound **1** (0.5 g, 1.28 mmol) and diethyl malonate (1.28 mmol) was refluxed for 3 h.



Scheme 3

The reaction mixture was cooled, treated with diethyl ether (50 mL), then the solid product was filtered off, washed with diethyl ether, dried, and recrystallized from methanol to afford compound **15** (Scheme 3). Color: Brown. Yield: 64.75%. M.p.: 174-176 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 1707 (C=O), 1646 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.11 (s, 2H, CH_2), 6.78-7.65 (m, 15H, 3Ph). MS (EI, *m/z* (%)):459 (M^+, 1.47), 441 (0.59), 431 (1.24), 418 (0.17), 414 (0.98), 408 (100), 398 (3.56), 382 (3.13), 373 (2.64), 356 (0.84), 349 (1.59), 307 (3.97), 281 (0.18), 253 (0.66), 231 (0.47), 178 (10.91), 152 (3.47), 110 (0.69), 103 (2.57), 86 (1.46), 77 (34.97), 76 (9.35), 51 (34.85). Anal. calcd. for $C_{28}H_{17}N_3O_4$: C, 73.20; H, 3.73; N, 9.15. Found: C, 73.48; H, 3.62; N, 9.38%.

2.2.19. Synthesis of 3-(hydroxymethylene)-7,8,9-triphenyl-2H-pyrimido[1,2-b]pyridazine-2,4(3H)-dione (16)

A solution of compound **1** (0.5 g, 1.28 mmol) in potassium hydroxide (10 mL, 50 %) and chloroform (10 mL) was refluxed for 12 h. The aq. layer was separated and acidified with hydrochloric acid. The solid product formed was filtered off, washed with water, and recrystallized from chloroform to give compound **16** as pale brown crystals (Scheme 3). Color: Pale brown. Yield: 70.92%. M.p.: 143-145 °C. FT-IR (KBr, ν, cm^{-1}): 3423 (OH), 3057 (CH, Arom.), 1714 (C=O), 1635 (C=N). MS (EI, *m/z* (%)):420 (M^+, 8.23), 402 (6.96), 391 (6.58), 350 (7.97), 337 (8.86), 277 (100), 267 (7.59), 191 (6.58), 152 (8.99), 143 (6.84), 82 (6.84), 76 (8.23), 69 (11.39). Anal. calcd. for $C_{26}H_{17}N_3O_3$: C, 74.45; H, 4.09; N, 10.02. Found: C, 74.63; H, 4.17; N, 10.18%.

2.2.20. Synthesis of 2-chloro-4-oxo-7,8,9-triphenyl-4H-pyrimido[1,2-b]pyridazine-3-carbaldehyde (17)

Method A: A solution of compound **1** (0.5 g, 1.28 mmol) in dimethylformamide (10 mL) and phosphoryl chloride (2 mL) was stirred at 60 °C for 2 h, then the reaction mixture was cooled, and poured into ice cold water (200 mL). The precipitate was filtered off, washed with water, dried, and recrystallized from acetone to give compound **17** (Scheme 3). Color: Dark brown. Yield: 69.73%. M.p.: 179-180 °C. FT-IR (KBr, ν, cm^{-1}): 3057 (CH, Arom.), 2925, 2854 (CH Aliph.), 1714 (C=O), 1635 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.60-7.66 (m, 15H, 3Ph), 10.22 (s, 1H, CHO). MS (EI, *m/z* (%)): 440 (M^+ +2, 0.2), 438 (M^+, 10.96), 410 (9.31), 409 (9.76), 401 (7.81), 397 (8.71), 361 (11.41), 348 (9.01), 333 (11.11), 277 (40.54), 161 (8.11), 104 (10.51), 89 (12.31), 77 (25.83), 64 (100). Anal. calcd. for $C_{26}H_{16}ClN_3O_2$: C, 71.31; H, 3.68; N, 9.60. Found: C, 71.69; H, 3.76; N, 9.74%.

Method B: A mixture of compound **16** (0.5 g, 1.19 mmol) and phosphoryl chloride (10 mL) was refluxed for 1 h. The reaction mixture was cooled, and poured into ice cold water (200 mL). The solid product was filtered off, washed with water, dried, and recrystallized from acetone to give compound **17** as dark brown crystals.

2.2.21. Measuring the antimicrobial activity of compounds (2-17)

Applying the agar plate diffusion technique [7], the newly synthesised compounds were screened for their antimicrobial activity against Gram positive bacteria (*Staphylococcus aureus*), Gram negative bacteria (*Escherichia coli*), yeast (*Candida albican*), and fungi (*Aspergillus flavus*). Briefly, 100 µL of the tested bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 10^8 cells/mL for bacteria or 10^5 cells/mL for fungi [8], 100 µL of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. The plates inoculated with filamentous fungi were incubated at 25 °C for 48 h, bacteria at 35-37 °C for 24-48 h, and yeast at 30 °C for 24-48 h. The diameters of the inhibition zones (the area of no growth of the organism around the disk) were measured in millimetersusing slipping calipers of National Committee for Clinical Laboratory Standards [9].

Table 1. Antimicrobial activity of the investigated conmpounds *.

Compound	Inhibition zone diameter (mm/mg) sample			
	Staphylococcus aureus (G^+)	*Escherichia coli* (G^-)	*Candida albicans*	*Aspergillus flavus*
2	++	++	-	-
3b	++	++	-	-
3c	++	++	-	-
3d	++	++	-	-
4	++	++	++	+
5	++	++	-	-
6	++	++	-	-
7	++	++	-	-
8	+++	++	++	-
10	++	++	+	-
13	++	++	-	-
15	++	++	-	-
16	++	++	-	-
17	++	++	-	-
Control: DMSO	-	-	-	-
Ampicillin (Antibacterial agent)	+++	++	-	-
Amphotericin B (Antifungal agent)	-	-	++	++

* Zone of inhibition: + = < 11 mm; ++ = 11-20 mm; +++ = 20-30 mm; - = no inhibition.

Standard discs of ampicillin (Antibacterial agent), amphotericin B (Antifungal agent) severed as positive controls for antimicrobial activity, but filter discs impregnated with 10 µL of dimethylsulfoxide were used as a negative control. Blank paper discs (Schleicher & Schuell, Spain) with a diameter of 8.0 mm were impregnated with 10 µL of tested concentration of the stock solution.

3. Results and discussion

3.1. Synthesis

It was reported that the reaction of 3-amino-4,5,6-triphenylpyridazine with malonic acid in presence of phosphoryl chloride led to the pyrimido[1,2-*b*]pyridazinone derivative, **1** [5]. The various reactions of the pyrimido pyridazinone derivative **1** are shown in Scheme 1. Chlorination of compound **1** with phosphoryl chloride led to the corresponding 2-chloro derivative, **2**. Taking the advantage of the reactivity of the 2-chloro atom in compound **2**, it was subjected to nucleophilic substitution reactions in order to prepare other derivatives of the system. Thus, reaction of compound **2** with sodium methanolate, ethanolate, sodium azide, and hydrazine hydrate, gave compounds **3a-d**, respectively (Scheme 1). Also, the chloro derivative **2** underwent thionation with thiourea in refluxing ethanol leading to thiouronium salt, which can be isolated. The 7,8,9-triphenyl-2-thioxo-2*H*-pyrimido[1,2-*b*]pyridazin-4(3*H*)-one (**4**) was obtained from the thiouronium salt in aqueous solution by basic hydrolysis followed by acidification with hydrochloric acid (Scheme 1).

Some other reactions of compound **1** are shown in (Scheme 2). Bromination with an excess of bromine, a dibromo derivative **5** was obtained. Chlorination of compound **1** with sulfuryl chloride led to 3,3-dichloro-7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-dione,**6**. The usefulness of the latter compound is demonstrated in (Scheme 2). The ring contraction of compound **6** was obtained on boiling with aqueous solution of sodium carbonate to afford 3-chloro imidazo[1,2-*b*]pyridazin-2(3*H*)-one, **7**. However, reaction of the compound **6** with zinc in acetic acid at refluxing temperature led to 3-chloro derivative **8** in a good yield, which underwent direct amination by fusion with ammonium acetate at 210 °C for 30 min to give 3-amino-7,8,9-triphenyl-2*H*-pyrimido[1,2-*b*]pyridazine-2,4(3*H*)-dione derivative **9**. The action of nitric acid in acetic acid could be performed using sodium nitrite as catalyst led to 3-nitropyrimidopyridazinone derivative**10**. The catalytic effect of sodium nitrite can be explained by an initial nitrosation of compound **1** in position 3 and subsequent oxidation of the nitroso group to the desired nitro group [10].Treatment of the nitro derivative **10** with phosphoryl chloride gave the corresponding 2-chloro derivative **11**. Also, reduction of compound **10** was carried out with zinc dust in acetic acid at refluxing temperature, and gave the 3-amino derivative **9** (Scheme 2).

Introduction of an acetyl group into the 3-position of the pyrimidopyridazinone derivative **1** was obtained by direct C-acetylation with acetic acid in polyphosphoric acid according to known method [11], gave 3-acetyl pyrimidopyridazinone derivative **12** in good yield. The α,β-unsaturated ketone **13** was synthesized employing Claisen-Schmidt reaction by treating the 3-acetyl derivative **12** with benzaldehyde in presence of base. Refluxing compound **12** with phosphoryl chloride gave the corresponding 3-acetyl-2-chloropyrimido pyridazinone derivative **14** (Scheme 3).

When the 1,3-dinucleophilic 7,8,9-triphenyl-2*H*-pyrimido [1,2-*b*]pyridazine-2,4(3*H*)-dione (**1**) was condensed with diethyl malonate at refluxing temperature, furnished pyrano pyrimidopyridazinone derivative **15** (Scheme 3). Formylation of compound **1** at position 3 was achieved by its reaction with chloroform/potassium hydroxide mixture, and afforded 3-(hydroxymethylidene)-7, 8, 9-triphenyl-2*H*-pyrimido[1, 2-*b*] pyridazine-2,4(3*H*)-dione, **16**. However, reaction of compound **1** with Vilsmeier reagent (dimethylformamide/phosphoryl chloride) led to 2-chloro-4-oxo-7,8,9-triphenyl-4*H*-pyrimido [1,2-*b*]pyridazine-3-carbaldehyde **17**, which was also obtained by the reaction of compound **16** with phosphoryl chloride at refluxing temperature (Scheme 3). The newly synthesized compounds were characterized by IR, NMR and mass spectrum as well as the elemental analysis, listed in experimental section. The spectral analyses were in accordance with the assigned structures.

3.2. Screening for antimicrobial activities

The given results in Table 1 revealed that compound **8** was highly active against *Staphylococcus aureus*. On the other hand, compounds **2**, **3b-d**, **4-7**, **10**, **13**, **15**, **16** and **17**) showed moderate activity against both *Staphylococcus aureus* and *Escherichia coli*. Also, the results indicated that compounds **4** and **8** showed moderate antifungal activity against *Candida albicans*. In general, the synthesised compounds showed moderate antimicrobial activity against the examined bacteria comparable with the standard antibacterial ampicillin.

4. Conclusion

A new series of pyrimidopyridazine bearing different substiutents were synthesized and biological evaluation compound **8** showed promising antibacterial activities, compared with the reference drugs.

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