

A convenient access to new pyrido[4,3-*d*]pyrimidine, thiazolo[3,4-*c*]pyrimidine and pyrimido[4,5-*d*]pyridazine derivatives

Nabila A. Kheder,^a Yahia N. Mabkhot,^b and Ahmad M. Farag^{a*}

^aDepartment of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

^bDepartment of Chemistry, Faculty of Science, King Saud University, 2455, Riyadh 11751, Saudi Arabia

E-mail: afarag49@yahoo.com

Abstract

Several new pyrido[4,3-*d*]pyrimidine, pyrimido[4,5-*d*]pyridazine and thiazolo[3,4-*c*]pyrimidine derivatives were prepared from the versatile, readily accessible ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate. Bromination of the latter compound afforded the corresponding 6-bromomethylpyrimidine derivative. Treatment of the latter with malononitrile or ethyl cyanoacetate afforded the corresponding hexahydrocyclopenta[*d*]pyrimidine derivatives **4a,b**. Reaction of the bromomethylpyrimidine with potassium cyanide followed by treatment with arenediazonium salt afforded the corresponding hydrazone **6** which reacts with hydrazine derivatives to afford the corresponding pyrido[4,3-*d*]pyrimidine derivatives **8a,b**. It reacts also with thiourea, thiosemicarbazide and phenylhydrazine to afford ethyl 3-imino-5-oxo-7-phenyl-3,5,6,7-tetrahydro-1-*H*-thiazolo[4,3-*c*]pyrimidine-8-carboxylate (**10a**), ethyl 3-hydrazono-5-oxo-7-phenyl-3,5,6,7-tetrahydro-1-*H*-thiazolo[3,4-*c*]pyrimidine-8-carboxylate (**10b**) and 4,6-diphenyl-3,4,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**12**), respectively. The antimicrobial activity of selected examples of the synthesized compounds was tested and showed moderate activity.

Keywords: 1,2,3,4-tetrahydropyrimidine, hexahydrocyclopenta[*d*]pyrimidine, pyrido[4,3-*d*]pyrimidine, thiazolo[3,4-*c*]pyrimidine, pyrimido[4,5-*d*]pyridazine

Introduction

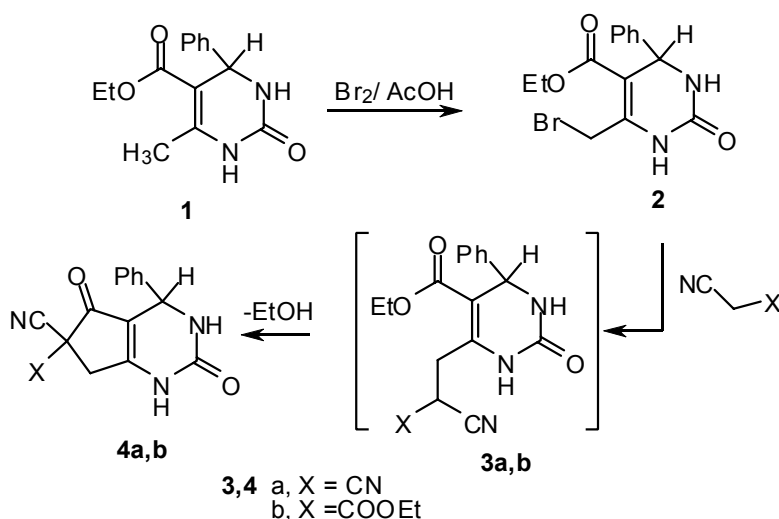
The pyrimidine nucleus is present in a wide range of bioactive natural products. In addition, the pharmacological and biological activities of pyrimidine derivatives are well documented.¹⁻⁶ Encouraged by these findings and as a continuation of our interest in the synthesis of a variety of heterocyclic systems for biological screening,⁷⁻¹⁷ we have found that 6-bromomethylpyrimidine **2**¹⁸ is a versatile, readily accessible building block for the synthesis of new

cyclopenta[*d*]pyrimidine, pyrido[4,3-*d*]pyrimidine, thiazolo[3,4-*c*]pyrimidine and pyrimido[4,5-*d*]pyridazine derivatives of expected biological potency. Our interest in the above point prompted us to react compound **2** with some nucleophiles.

Results and Discussion

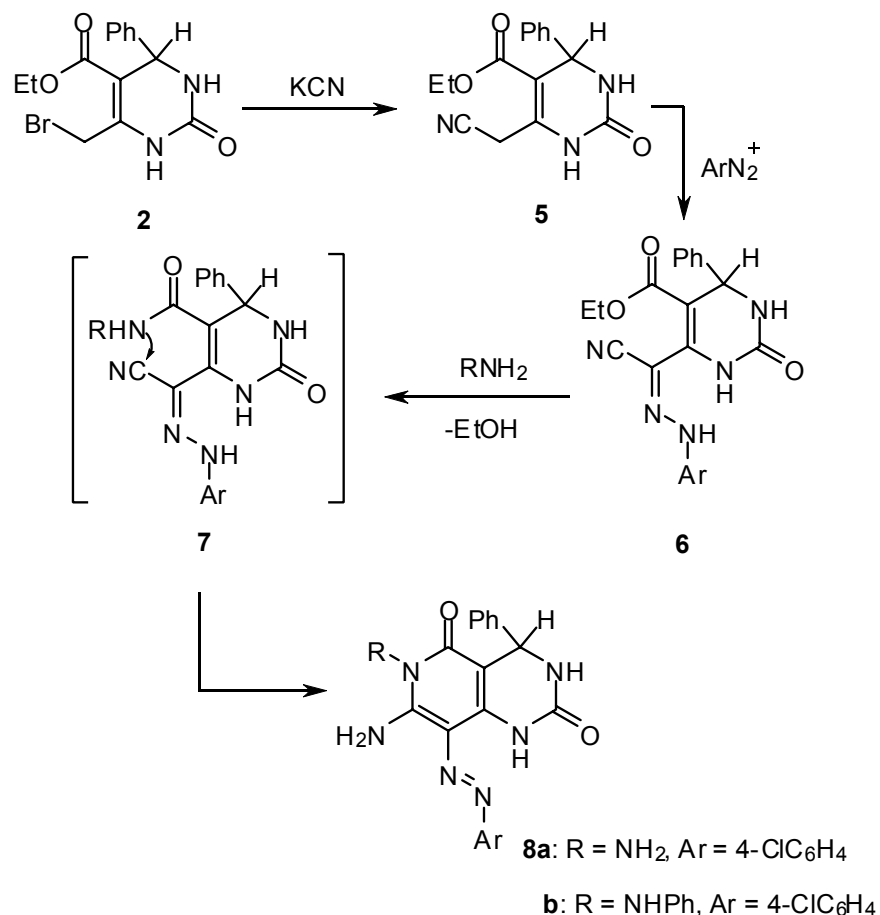
The versatile synthon ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**),¹⁸ was obtained via bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**)¹⁹ in acetic acid. Treatment of the compound **2** with malononitrile or with ethyl cyanoacetate afforded the corresponding hexahydrocyclopenta[*d*]pyrimidine derivatives **4a** and **4b**, respectively (Scheme 1).

This reaction is assumed to proceed *via* nucleophilic attack of a carbanion-methylene group, in malononitrile or ethyl cyanoacetate, on the 6-bromomethyl group in **2** to afford the non-isolable intermediates **3a,b** which underwent intramolecular cyclization through elimination of ethanol to afford the final products **4a,b**. The structure of the products **4a,b** was determined from spectroscopic as well as elemental analytical data. Thus, compound **4a**, taken as a typical example, showed absorption bands at 1650, 1696, 2195, 2210, 3102, 3350 cm⁻¹ corresponding to two C=O groups, two C≡N and two NH functions, respectively. Its ¹H NMR spectrum revealed the absence of CH₃ and CH₂ protons of ethoxycarbonyl group and showed signals at δ 4.82 and 5.25 due to CH₂, CH protons, respectively. It showed also two D₂O-exchangeable signals at δ 7.75 and 9.97 ppm corresponding to two NH protons, in addition to an aromatic multiplet in the region δ 7.26-7.39.



Scheme 1

6-Bromomethylpyrimidine **2** underwent nucleophilic substitution reaction upon treatment with potassium cyanide to afford ethyl 6-cyanomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5**). The latter product couples smoothly with 4-chlorobenzenediazonium chloride to afford the corresponding hydrazone **6** (Scheme 2).



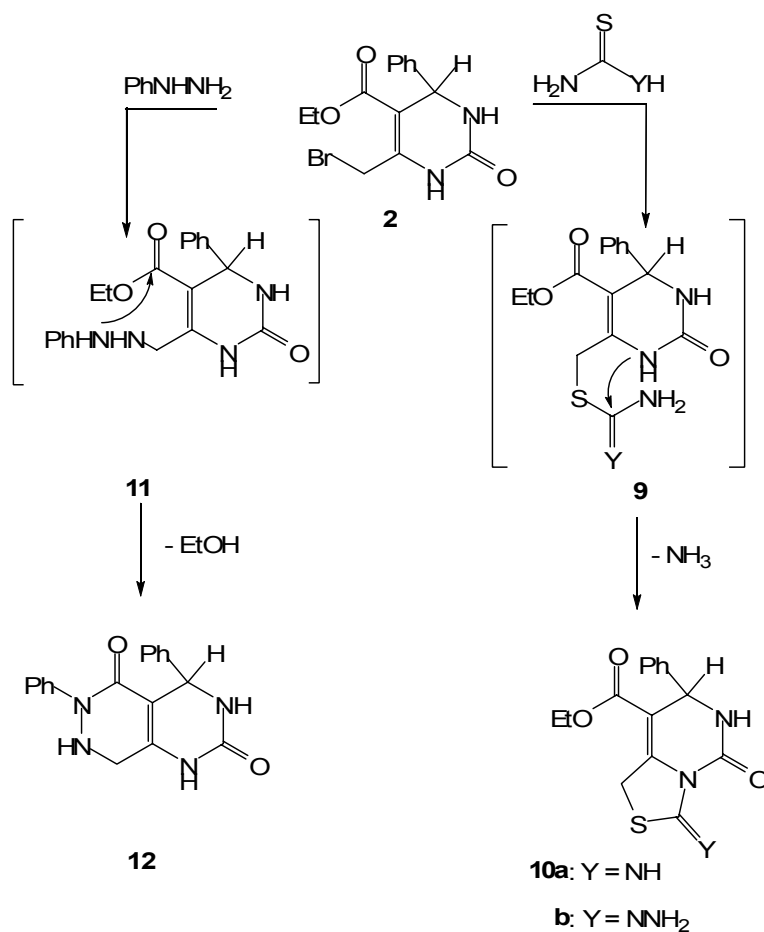
Scheme 2

The structures of compounds **5** and **6** were characterized from their spectroscopic as well as elemental analytical data. Thus, the IR spectrum of compound **5** revealed absorption bands at 3230, 3190, 2150, 1730 and 1645 cm⁻¹ corresponding to two C=O groups, C≡N and two NH functions, respectively. Its ¹H NMR spectrum showed a triplet signal at δ 1.10 (*J* = 7.2 Hz) corresponding to CH₃ protons, a quartet signal at δ 4.00 (*J* = 7.2 Hz) due to CH₂ protons, a singlet signal at δ 4.25 due to CH₂ protons, a doublet signal at δ 5.22 (*J* = 3.3 Hz) corresponding to CH-4 proton, an aromatic multiplet in the region 7.24-7.35, and two D₂O-exchangeable signals at δ 7.55 and 9.05 due two NH protons. The IR spectrum of compound **6** showed absorption bands at 1630, 1690, 2206, 3094, 3225 and 3271 cm⁻¹ corresponding to two C=O groups, C≡N and three NH functions, respectively. The ¹H NMR spectrum of the same

compound revealed a triplet signal at δ 1.09 ($J = 7.2$ Hz) due to CH_3 protons, a quartet signal at δ 4.06 ($J = 7.2$ Hz) due to CH_2 protons, and a doublet signal at δ 5.23 ($J = 3.3$ Hz) due to the CH -4 proton. It showed also three D_2O -exchangeable signals at δ 7.91, 9.46 and 11.60 due to three NH protons, in addition to an aromatic multiplet in the region 7.28-7.53.

When the hydrazone **6** was treated with hydrazine hydrate or with phenylhydrazine, it afforded the corresponding pyrido[4,3-*d*]pyrimidine derivatives **8a** and **8b**, respectively (Scheme 2). The structures of the products **8a** and **8b** were characterized from their spectroscopic as well as elemental analytical data. For example, the IR spectrum of compound **8a** revealed the absence of an absorption band corresponding to the $\text{C}\equiv\text{N}$ function and showed absorption bands at 1659, 1690, 3105-3410 cm^{-1} corresponding to two $\text{C}=\text{O}$, NH_2 and two NH functions, respectively. Its ^1H NMR spectrum revealed the absence of signals corresponding to CH_3 and CH_2 protons of the ethoxy group and showed a singlet signal at δ 5.46 due to the CH proton and three D_2O -exchangeable signals at δ 5.77, 7.80 and 11.0 corresponding to NH_2 and two NH protons, respectively, in addition to an aromatic multiplet and NH_2 in the region δ 7.29-7.62.

The behavior of compound **2** towards phenylhydrazine as a nitrogen nucleophile was also investigated. Thus, when **2** was treated with phenylhydrazine, it afforded 4,6-diphenyl-3,4,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**12**) (Scheme 3). The structure of the isolated product **12** was evidenced by its spectroscopic and elemental analysis data. Thus, its IR spectrum exhibited absorption bands at 1665, 1687, 3010, 3120 and 3255 cm^{-1} corresponding to two $\text{C}=\text{O}$ groups, and three NH functions, respectively. Moreover, its ^1H NMR spectrum revealed the absence of signals corresponding to CH_3 and CH_2 protons of an ethoxy group and revealed signals at δ 4.38 and 5.19 due to CH_2 , CH protons and three D_2O -exchangeable signals at δ 7.61, 9.26 and 9.55 corresponding to three NH protons, in addition to an aromatic multiplet in the region δ 6.88-7.22.



Scheme 3

Conclusions

In conclusion, we have investigated the synthetic potency of 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**) as a versatile, readily accessible building block for the synthesis of new fused heterocyclic compounds of biological and pharmaceutical importance.

Experimental Section

General Procedures. All melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded of samples in KBr on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. ¹H spectra were run at 300 MHz and ¹³C spectra were run at 75.46 MHz in dimethyl sulphoxide (DMSO-*d*₆). Chemical shifts were related to that of the solvent. Mass

spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The biological evaluation of the products **4a**, **8a**, **8b** and **12b** were carried out at the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**),¹⁹ ethyl 6-bromomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**)¹⁸ were prepared following the literature procedures.

Reaction of 6-bromomethylpyrimidine **2** with malononitrile and with ethyl acetoacetate. General procedure

To an ethanolic solution of 6-bromomethylpyrimidine **2**¹⁸ (0.34 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) or with ethyl cyanoacetate (0.113 mL, 1 mmol) was added few drops of piperidine and the reaction mixture was refluxed for 4 h. The solid product was collected by filtration, washed with ethanol and purified by crystallisation from DMF to afford the corresponding cyclopenta[*d*]pyrimidine derivatives **4a** and **4b**, respectively.

2,5-Dioxo-4-phenyl-3,4,5,7-tetrahydro-1-*H*-cyclopenta[*d*]pyrimidine-6,6(2*H*)-dicarbonitrile (4a**).** Yield (70.21%); mp. 290-1 °C; IR (KBr) ν 3350 (NH), 3102 (NH), 2210 (C \equiv N), 2195 (C \equiv N), 1696 (C=O), 1650 (C=O) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 4.82 (s, 2H, CH₂), 5.25 (d, 1H, CH, *J* = 3.3 Hz), 7.26-7.39 (m, 5H, ArH's), 7.75 (s, 1H, D₂O-exchangeable, NH), 9.97 (s, 1H, D₂O-exchangeable, NH). For C₁₅H₁₀O₂N₄ Calcd.: C, 64.74; H, 3.62; N, 20.13. Found: C, 64.65; H, 3.67; N, 20.08%.

Ethyl 6-cyano-2,5-dioxo-4-phenyl-2,3,4,5,6,7-hexahydro-1-*H*-cyclopenta[*d*]pyrimidine-6-carboxylate (4b**).** Yield (69.87%); mp. 285-6 °C; IR (KBr) ν 3312 (NH), 3220 (NH), 2210 (C \equiv N), 1690 (C=O), 1635 (C=O) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.14 (t, 3H, CH₃, *J* = 7.2 Hz), 4.1 (q, 2H, CH₂, *J* = 7.2 Hz), 4.68 (s, 2H, CH₂), 5.24 (d, 1H, CH, *J* = 3.3 Hz), 7.32-7.41 (m, 5H, ArH's), 7.73 (s, 1H, D₂O-exchangeable, NH), 9.88 (s, 1H, D₂O-exchangeable, NH). For C₁₇H₁₅O₄N₃ Calcd.: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.72; H, 4.68; N, 12.92%.

Ethyl 6-cyanomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5**)

A mixture of 6-bromomethylpyrimidine **2** (0.34 g, 1 mmol) in EtOH (10 mL) and potassium cyanide (0.65 g, 1 mmol) in water (1 mL) was heated under reflux for 1h then left to cool. The reaction mixture was poured onto ice-cold water (30 mL). The solid precipitate was filtered off, washed with water and dried. Recrystallization from EtOH/water afforded the cyanomethyl derivative **5** in 60% yield, mp. 170 °C; IR (KBr) ν 3230 (NH), 3190 (NH), 2150 (C \equiv N), 1730 (C=O), 1645 (C=O) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.1 (t, 3H, CH₃, *J* = 7.2 Hz), 4.0 (q, 2H, CH₂, *J* = 7.2 Hz), 4.25 (s, 2H, CH₂), 5.22 (d, 1H, CH, *J* = 3.3 Hz), 7.24-7.35 (m, 5H, ArH's), 7.55 (s, 1H, D₂O-exchangeable, NH), 9.05 (s, 1H, D₂O-exchangeable, NH). For C₁₅H₁₅O₃N₃ Calcd.: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.14; H, 5.29; N, 14.68%.

Synthesis of ethyl 6-[(2-(4-chlorophenyl)hydrazono)(cyano)methyl]-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6)

To a cold solution of the cyanomethyl derivative **5** (2.85 g, 10 mmol) in ethanol (50 mL) and sodium acetate trihydrate (3 g) was added an equimolar amount of the diazonium chloride of 4-chloroaniline [prepared by diazotizing 4-chloroaniline (1.45 g, 10 mmol) in hydrochloric acid (6 M, 3 mL) with sodium nitrite solution (0.7 g, 10 mmol) in 5 mL water]. The addition, was carried out portionwise with stirring at 0-5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4 h then kept in an ice chest for 12 h and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from acetic acid to afford the hydrazone derivative **6** in 79% yield, mp. 240-1 °C; IR (KBr) ν 3271 (NH), 3225 (NH), 3094 (NH), 2206 (C \equiv N), 1690 (C=O), 1630 (C=O) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.09 (t, 3H, CH₃, J = 7.2 Hz), 4.06 (q, 2H, CH₂, J = 7.2 Hz), 5.23 (d, 1H, CH, J = 3.3 Hz), 7.3-7.5 (m, 9H, ArH's), 7.9 (s, 1H, D₂O-exchangeable, NH), 9.48 (s, 1H, D₂O-exchangeable, NH), 11.63 (s, 1H, D₂O-exchangeable, NH); ^{13}C NMR (DMSO- d_6) δ 13.59, 53.81, 60.21, 102.49, 107.15, 111.05, 116.89, 121.12, 126.08, 127.68, 128.55, 129.03, 140.36, 141.48, 143.43, 151.90, 164.33. For C₂₁H₁₈O₃N₅Cl Calcd.: C, 59.51; H, 4.28; N, 16.52. Found: C, 59.48; H, 4.26; N, 16.49%.

Synthesis of 6,7-Disubstituted-8-(4-chlorophenylazo)-4-phenyl-3,4-dihydropyrido- [4,3-*d*]pyrimidine-2,5-(1*H*, 6*H*)-dione derivatives 8a,b. General procedure

To a solution of the hydrazone **6** (0.85 g, 2 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 mL, 2 mmol) or phenylhydrazine (0.216 g, 2 mmol) was added and the reaction mixture was refluxed for 4 h, then allowed to cool. The solid product that formed was filtered off, washed with EtOH, and dried. Recrystallization from DMF/EtOH, afforded the corresponding pyrido[4,3-*d*]pyrimidine derivatives **8a** and **8b**, respectively.

6,7-Diamino-8-(4-chlorophenylazo)-4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidine-2,5-(1*H*, 6*H*)-dione (8a). Yield (79%); mp. > 300 °C; IR (KBr) ν 3410, 3233, 3170, 3105 (NH₂, 2NH), 1690 (C=O), 1659 (C=O) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 5.46 (d, 1H, CH, J = 2.7 Hz), 5.77 (s, 2H, D₂O-exchangeable NH₂), 7.29-7.37 (m, 7H, ArH+ NH₂), 7.46 (d, 2H, J = 8.7 Hz), 7.62 (d, 2H, J = 8.7 Hz), 7.80 (s, 1H, D₂O-exchangeable, NH), 11.00 (s, 1H, D₂O-exchangeable, NH); ^{13}C NMR (DMSO- d_6) δ 52.53, 111.60, 126.34, 127.22, 127.71, 127.86, 128.32, 128.56, 132.16, 137.97, 139.60, 142.40, 143.32, 151.10, 156.93. For C₁₉H₁₆O₂N₇Cl Calcd.: C, 55.68; H, 3.94; N, 23.92; Cl, 8.65. Found: C, 55.61; H, 3.97; N, 23.95; Cl, 8.63%.

7-Amino-8-((4-chlorophenyl)azo)-4-phenyl-6-(phenylamino)-3,4-dihydropyrido[4,3-*d*]pyrimidine-2,5-(1*H*,6*H*)dione (8b). Yield (80%); mp. 254-5 °C; IR (KBr) ν 3320, 3210, 3190 (NH), 1665 (C=O), 1625 (C=O) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 5.49 (d, 1H, CH, J = 2.4 Hz), 6.26 (s, 2H, D₂O-exchangeable NH₂), 6.77 (m, 1H), 6.96 (d, 2 H), 7.21-7.40 (m, 7H), 7.48 (d, 2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.4 Hz), 8.14 (s, 1H, D₂O-exchangeable, NH), 8.88 (s, 1H, D₂O-exchangeable, NH), δ 10.91 (s, 1H, D₂O-exchangeable, NH); ^{13}C NMR (DMSO- d_6) δ 52.60, 109.26, 111.73, 118.92, 126.42, 127.32, 127.46, 127.91, 128.34, 128.59, 129.26, 132.26, 137.78,

139.58, 141.07, 142.30, 145.46, 151.05, 156.94. For $C_{25}H_{20}O_2N_7Cl$ Calcd.: C, 61.79; H, 4.15; N, 20.18; Cl, 7.30. Found: C, 61.72; H, 4.08; N, 20.13; Cl, 7.28%.

Ethyl 3-substituted-3,5,6,7-tetrahydro-5-oxo-7-phenyl-1H-thiazolo[3,4-c]pyrimidine-8-carboxylate 10a,b. General procedure

To a solution of the 6-bromomethylpyrimidine derivative **2** (0.68 g, 2 mmol) in EtOH (20 mL), thiourea (0.152 g, 2 mmol) or thiosemicarbazide (0.184 g, 2 mmol) was added and the reaction mixture was refluxed for 4h, then allowed to cool. The solid product was collected by filtration, washed with EtOH and crystallised from EtOH to afford the corresponding thiazolo[3,4-c]pyrimidine **10a** and **10b**, respectively.

Ethyl 3-imino-5-oxo-7-phenyl-3,5,6,7-tetrahydro-1-H-thiazolo[3,4-c]pyrimidine-8-carboxylate (10a). Yield (59%); mp.197-9 °C; IR (KBr) ν 3215 (NH), 3190 (NH), 1720 (C=O), 1670 (C=O) cm^{-1} ; 1H NMR (DMSO- d_6) δ 0.90 (t, 3H, CH_3 , $J = 7.2$ Hz), 4.15 (q, 2H, CH_2 , $J = 7.2$ Hz), 4.9 (s, 2H, CH_2), 5.3 (s, 1H, CH), 7.12-7.57 (m, 5H, ArH's), 9.35 (s, 1H, D_2O -exchangeable, NH), 11.97 (s, 1H, D_2O -exchangeable, NH). For $C_{15}H_{15}O_3N_3S$ Calcd.: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.73; H, 4.80; N, 13.23; S, 10.06%.

Ethyl 3-hydrazono-5-oxo-7-phenyl-3,5,6,7-tetrahydro-1-H-thiazolo[3,4-c]pyrimidine-8-carboxylate (10b). Yield (66%); mp.192 °C; IR (KBr) ν 3285 (NH), 3205-3175 (NH_2), 1720 (C=O), 1670 (C=O) cm^{-1} ; 1H NMR (DMSO- d_6) δ 0.97 (t, 3H, CH_3 , $J = 7.2$ Hz), 4.18 (q, 2H, CH_2 , $J = 7.2$ Hz), 4.50 (s, 2H, CH_2), 5.14 (s, 1H, CH), 7.08-7.45 (m, 5H, ArH's), 8.55 (s, 1H, D_2O -exchangeable, NH_2), 11.56 (s, 1H, D_2O -exchangeable, NH). For $C_{15}H_{16}O_3N_4S$ Calcd.: C, 54.20; H, 4.85; N, 16.86; S, 9.65. Found: C, 54.28; H, 4.88; N, 16.82; S, 9.63%.

4,6-Diphenyl-3,4,7,8-tetrahydropyrimido[4,5-d]pyridazine-2,5-(1H, 6H)-dione (12).

To a solution of compound **2** (0.68 g, 2 mmol) in EtOH (20 mL), phenylhydrazine (0.216 g, 2 mmol) was added and the reaction mixture was refluxed for 4 h then allowed to cool. The solid product was collected by filtration, washed with EtOH and crystallised from DMF/EtOH to afford **12** in 60% yield; mp 275-7 °C; IR (KBr) ν 3255 (NH), 3120 (NH), 3010 (NH), 1687 (C=O), 1665 (C=O) cm^{-1} . 1H NMR (DMSO- d_6) δ 4.38 (s, 2H, CH_2), 5.19 (s, 1H, CH), 6.88-7.22 (m, 10H, ArH's), 7.61 (s, 1H, D_2O -exchangeable, NH), 9.26 (s, 1H, D_2O -exchangeable, NH), 9.55 (s, 1H, D_2O -exchangeable, NH); ^{13}C NMR (DMSO- d_6) δ 49.73, 51.90, 99.53, 116.23, 121.58, 126.31, 127.19, 128.06, 128.78, 143.34, 143.49, 150.41, 151.30, 165.48. For $C_{18}H_{16}O_2N_4$ Calcd.: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.52; H, 5.00; N, 17.52%.

Antimicrobial Activity

Compounds **4a**, **8a**, **8b** and **12b** were tested for their antimicrobial activities using four fungal species, namely *Aspergillus fumigatus* AF, *Penicillium italicum* PI, *Syncephalastrum racemosum* SR and *Candida albicans* CA. Also, four bacteria species namely, *Staphylococcus aureus* SA, *Pseudomonas aeruginosa* PA, *Bacillus subtilis* BS and *Escherichia coli* EC were tested. The organisms were tested against the activity of solutions of concentration of 1 mg/ mL, 2.5 mg/ mL and 5 mg/ mL of each compound and using an inhibition zone diameter in cm (IZD) as criterion

for the antimicrobial activity. The fungicide Terbinafin and the bactericide Chloramphenicol were used as references to evaluate the potency of the tested compounds under the same conditions. The results are summarized in Table 1.

The test results revealed that all compounds exhibited a moderate activity against *Staphylococcus aureus* (SA), *Bacillus subtilis* (BS) and *Escherichia coli* (EC) at concentrations of 5, 2.5 and 1 mg/ mL. All compounds exhibited almost no activity against *Aspergillus fumigatus* (AF), *Penicillium italicum* (PI), *Syncephalastrum racemosum* (SR), *Candida albicans* (CA) and *Pseudomonas aeruginosa* (PA).

Table 1. Antimicrobial activity of compounds **4a**, **8a**, **8b** and **12**

Sample	4a			8a			8b			12			Standard mg/ mL		
	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
(AF)	0	0	0	0	0	0	0	0	0	0	0	0	+++	+++	++
(PI)	0	0	0	0	0	0	0	0	0	0	0	0	+++	+++	++
(SR)	0	0	0	0	0	0	0	0	0	0	0	0	+++	+++	+++
(CA)	0	0	0	0	0	0	0	0	0	0	0	0	++	++	++
(SA)	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
(PA)	0	0	0	0	0	0	0	0	0	0	0	0	+++	+++	++
(BS)	++	++	++	++	++	++	++	++	++	++	++	++	+++	+++	++
(EC)	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++

Micro-organism/IZD (cm)*.

*IZD beyond control/(sign): 1.1-1.5 cm/(+++); 0.6-1.0 cm/(++); 0.1-0.5 cm/(+); 0 cm/(0).

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