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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW PYRIMIDINE DERIVATIVES

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Abstract- The utility of ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**1**) in the synthesis of some new pyrido[1,2-*f*]pyrimidine, pyrazolo-[3,4-*b*]pyrido[1,2-*f*]pyrimidine, 6-(4-substituted styryl)pyrimidine, pyrido[4,3-*d*]-pyrimidine, pyrimido[5,4-*d*]pyridazine and substituted-6-(thien-2-yl)pyrimidine derivatives is reported. Antimicrobial evaluation of some selected examples from the synthesized products was carried out.

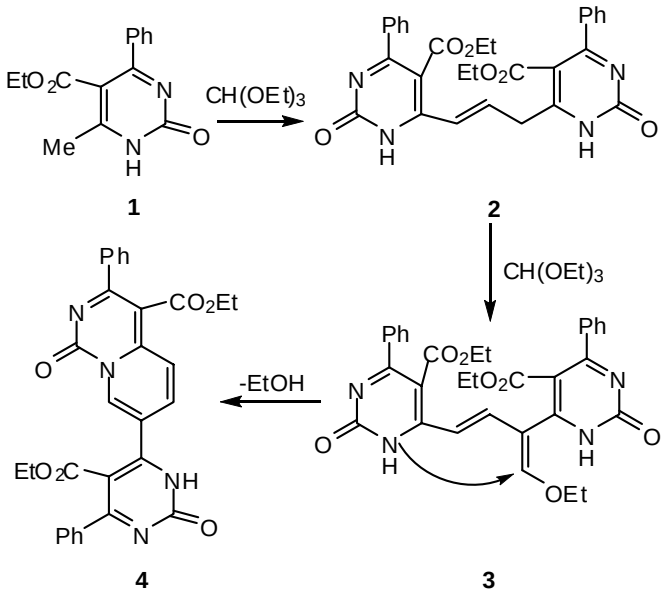
INTRODUCTION

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] As part of ongoing investigation aimed at the synthesis of a variety heterocyclic systems for biological and pharmacological evaluations,[7-18] we have found that ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-5-carboxylate (**1**), is a versatile, readily accessible building block for the synthesis of several new heterocyclic compounds of biological potency.

RESULTS AND DISCUSSION

Heating of 1,2-dihydropyrimidine derivative **1** with triethyl orthoformate afforded a product identified as ethyl 7-(5-ethoxycarbonyl-2,3-dihydro-2-oxo-6-phenylpyrimidine-4-yl)-1-oxo-3-phenyl-1*H*-pyrido[1,2-*f*]pyrimidine-4-carboxylate (**4**) (Scheme 1). The IR spectrum of the latter product revealed absorption bands at 1666, 1715 and 3355 cm^{-1} corresponding to two carbonyl and imino groups, respectively. Its ^1H NMR spectrum revealed a triplet signal at δ 0.79 (*J value* = 7.2 Hz) due to two CH_3 protons and a quartet signal at δ 3.89 (*J value* = 7.2 Hz) due to two CH_2 protons, in addition to D_2O-exchangeable

signal at δ 10.80 due to NH proton and an aromatic multiplet in the region δ 7.41-8.21. Also, its mass spectrum revealed a molecular ion peak at *m/z* 536.



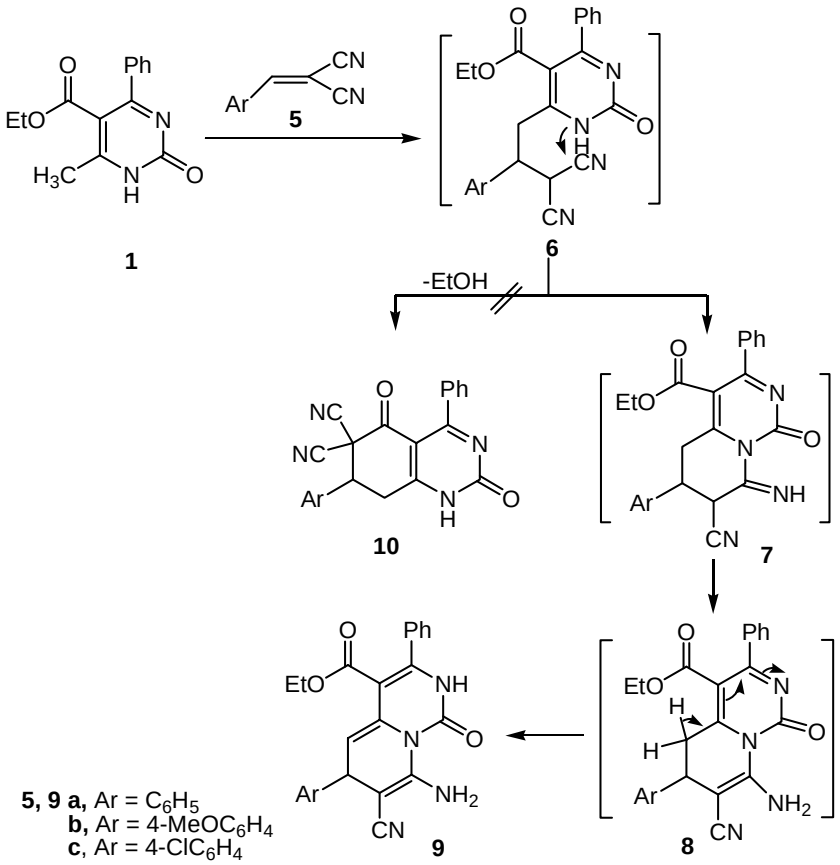
Scheme 1

Ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**1**) reacts with arylmethylene-propanedinitriles **5a-c**, in the presence of a catalytic amount of pipredine, to afford the corresponding pyrido[1,2-*f*]pyrimidine derivatives **9a-c** (Scheme 2). The IR spectrum of compound **9c**, taken as a typical example of the prepared series, revealed absorption bands at 1675, 1715, 2195, 3110, 3220 and 3355 cm^{-1} corresponding to two carbonyl groups, nitrile, amino and imino functions, respectively. Its ^1H NMR spectrum revealed a triplet signals at δ 0.74 (*J value* = 6.9 Hz) due to CH_3 protons, a quartet signal at δ 3.84 (*J value* = 6.9 Hz) due to CH_2 protons, two doublets at δ 4.25 and 5.25 (*J value* = 6.0 Hz) due to two CH protons and two D_2O-exchangeable signals at δ 6.88, 10.50 due to amino and imino protons, respectively, in addition to an aromatic multiplet in the regioṇ 7.28-7.47. Its mass spectrum showed a molecular ion peak at *m/z* 446.

Treatment of the pyrido[1,2-*f*]pyrimidine **9c** with hydrazine hydrate afforded the corresponding 1,2-dihydropyrazolo[3,4-*b*]pyrido[1,2-*f*]pyrimidine derivative **14** (Scheme 3). The IR spectrum of the latter product revealed absorption bands at 1659, 1703, 3040, 3215 and 3325 cm^{-1} corresponding to two carbonyl groups, imino function and amino group, respectively. Also, its ^1H NMR spectrum showed a triplet signal at δ 0.77 (*J value* = 6.9 Hz) due to CH_3 protons, a quartet signal at δ 3.88 (*J value* = 6.9 Hz) due to CH_2 protons, two D_2O-exchangeable signals at δ 6.15, 9.35 due to amino and imino protons, respectively, in addition to an aromatic multiplet in the region 7.31-7.49.

Treatment of 6-methylpyrimidine **1** with the appropriate aromatic aldehydes in the presence of catalytic amount of $ZnCl_2$, afforded the corresponding 6-(4-substituted styryl)pyrimidine derivatives **16a-c**

(Scheme 4).



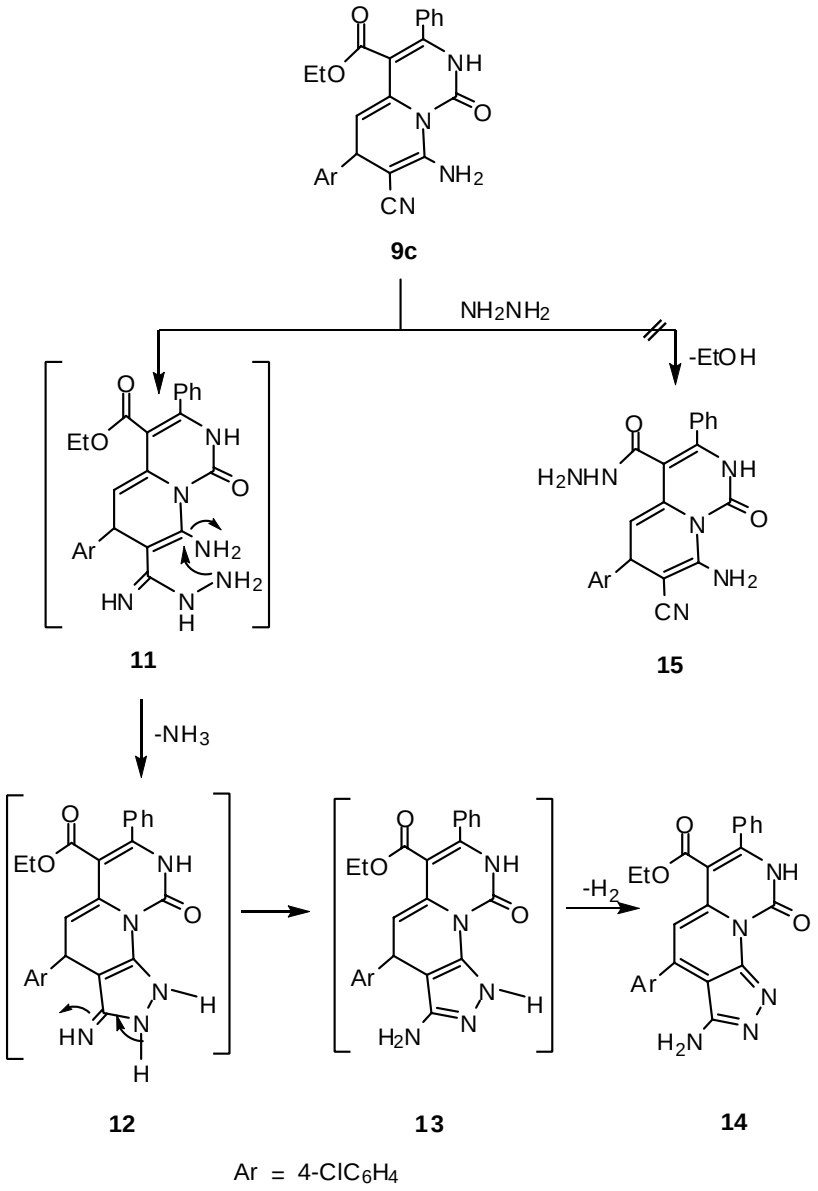
Scheme 2

The IR spectrum of **16c**, taken as a typical example of the prepared series, showed absorption bands at 1655, 1715 and 3215 cm^{-1} due to two carbonyl groups and imino function, respectively. Its ^1H NMR spectrum revealed a triplet signal at δ 0.87 (*J value* = 7.2 Hz) due to CH_3 protons and a quartet signal at δ 4.05 (*J value* = 7.2 Hz) due to CH_2 protons, two doublets at δ 7.25 and 7.39, with *J value* = 16 Hz, due to two CH protons and D_2O-exchangeable signal at δ 12.32 due to imino proton, in addition to an aromatic multiplet in the region 7.50-7.70.

When the pyrimidine derivative **16c** was treated with hydrazine hydrate it afforded the corresponding pyrido[4,3-*d*]pyrimidine derivative **19** (Scheme 4). The IR spectrum of the latter product showed absorption bands at 1675, 1697, 3350, 3240 and 3105 cm^{-1} due to two carbonyl, imino function and amino groups, respectively. Its ^1H NMR spectrum revealed broad D_2O-exchangeable signals at δ 4.59 and 11.35 corresponding to amino and imino protons, respectively, in addition to an aromatic multiplet in the region 6.72-7.32.

In a similar manner, the pyrimidine derivative **16c** reacts with phenylhydrazine to afford the corresponding pyridopyrimidine **22** (Scheme 4). The IR spectrum of compound **22** showed absorption bands at 1640, 1685, 3120 and 3250 cm^{-1} due to two carbonyl and two imino groups, respectively. Its ^1H NMR spectrum revealed two D_2O-exchangeable signals at δ 10.30 and 11.38 due to two imino protons,

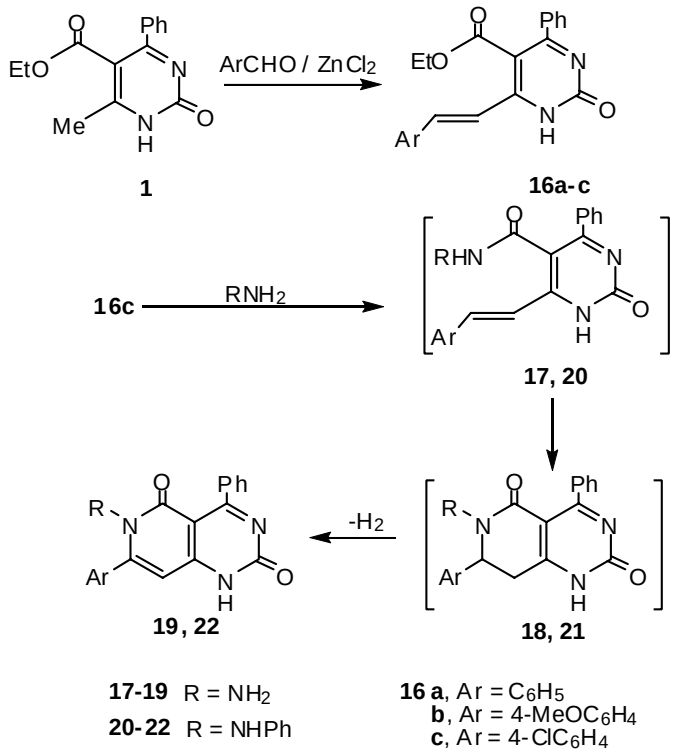
in addition to an aromatic multiplet in the region 7.31-7.69.



Scheme 3

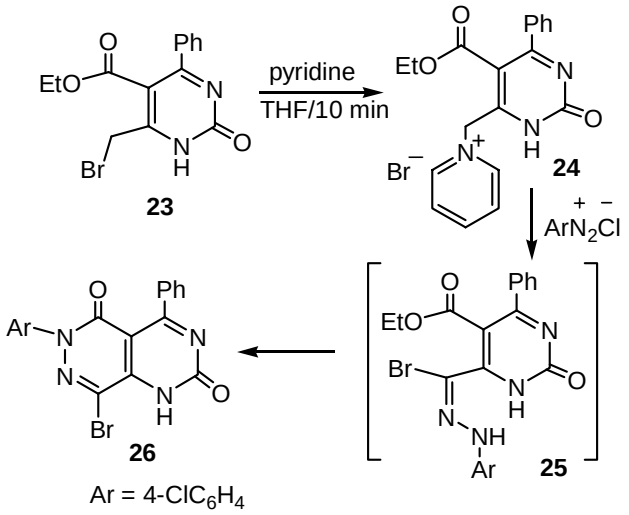
Treatment of ethyl 6-(bromomethyl)-1,2-dihydro-2-oxo-4-phenylpyrimidine-5-carboxylate **(23)** [21] with an equivalent amount of pyridine in dry THF afforded the pyridinium salt **24** (Scheme 5). The structure of the latter product was supported by its elemental analysis and spectral data [see experimental part]. The pyridinium salt **24** coupls smoothly with diazotized 4-chloroaniline in ethanol, buffered with sodium acetate to afford the corresponding 8-bromo-6-(4-chlorophenyl)-4-phenyl-1*H*,6*H*-pyrimido[5,4-*d*]pyridazine-2,5-dione (**26)** (Scheme 5).

The IR spectrum of the latter product revealed two absorption bands at 1636 and 1674 cm^{-1} due to two carbonyl groups and only one absorption at 3290 cm^{-1} corresponding to imino function. Its ^1H NMR spectrum showed a D_2O-exchangeable signal at δ 8.85 due to NH proton, in addition to an aromatic multiplet in the region δ 7.32-9.47. Its mass spectrum revealed a molecular ion peak at *m/z* 430.



Scheme 4

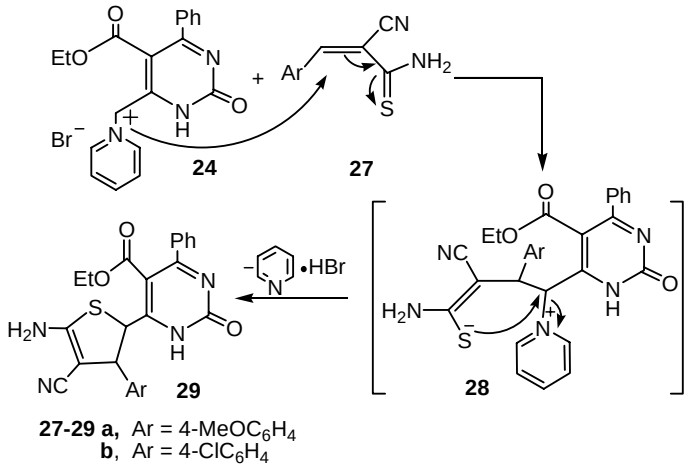
The pyridinium salt **24** reacts also with the 2-cyano-2-arylmethylenethioacetamide derivatives **27a,b**, in the presence of a catalytic amount of pipredine, to afford the corresponding 6-(5-amino-4-cyano-3-aryl-2,3-dihydrothiophen-2-yl)-5-ethoxycarbonyl-2-oxo-4-phenyl-1,2-dihydropyrimidine derivatives **29a,b** (Scheme 6).



Scheme 5

The IR spectrum of compound **29a**, taken as a typical example of the series prepared, revealed absorption bands at 1666, 1705, 2175, 3194, 3310 and 3395 cm^{-1} corresponding to two carbonyl, nitrile, amino and imino function, respectively. Its ^1H NMR spectrum revealed a triplet signal at δ 0.69 (J = 6.9 Hz) due to CH_3 protons, a quartet signal at δ 3.74 (J = 6.9 Hz) due to CH_2 protons, at δ 3.80 due to methoxy

protons, two doublets at δ 4.73 and 4.90 (J = 3.9 Hz) due to two CH protons and two D_2O-exchangeable signals at δ 6.92 and 12.60 due to amino and imino protons, respectively, in addition to an aromatic multiplet in the region 6.91-7.55. Its mass spectrum showed a fragment at *m/z* 474 corresponding to its molecular ion.



Scheme 6

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded on potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6). Chemical shifts are quoted in δ and were related to that of the solvents. The mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometers at 70 e.V. Elemental analyses were carried out at the Micro-analytical Center of Cairo University.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**1**),[19] arylmethylenepropane-dinitrile **5a-c**,[20] ethyl 6-bromomethyl-5-ethoxycarbonyl-2-oxo-4-phenyl-1,2-dihydropyrimidine (**23**) [21] and 2-cyano-2-arylmethylenethioacetamide derivatives **27a,b**[22] were prepared following the literature procedure. The biological evaluation of the products **9b, 9c, 14** and **26** were carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt.

Ethyl 7-(5-ethoxycarbonyl-2,3-dihydro-2-oxo-6-phenylpyrimidine-4-yl)-1-oxo-3-phenyl-1H-pyrido[1,2-f]pyrimidine-4-carboxylate (4)

A suspension of pyrimidine **1** (0.516 g, 2 mmol) in triethyl orthoformate (10 mL) was refluxed for 4h. The excess reagent was evaporated under reduced pressure and the remaining residue was triturated with

EtOH (20 mL). The solid product so formed was filtered off, washed with EtOH and dried. Recrystallization from DMF afforded orange crystals of **4** in 72% yield; mp 284-285 ºC; IR (KBr) υ 3355 (NH), 1715 (C=O), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.79 (t, 6H, $2CH_3$, J = 7.2 Hz), 3.89 (q, 4H, $2CH_2$, J = 7.2 Hz), 7.41-8.21 (m, 13H, ArH's), 10.80 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 539 (4.9%), 537 (3.2%), 536 (M^+, 16.3%). Anal. Calcd for $C_{30}H_{24}N_4O_6$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.20; H, 4.48; N, 10.40%.

Ethyl 8-amino-6-aryl-7-cyano-3-phenyl-2,6-dihydro-1-oxo-1H-pyrido[1,2-f]pyrimidine-4-carboxylate 9a-c.

General procedure:

A mixture of pyrimidine **1** (0.258 g, 1 mmol) and the appropriate arylmethylenepropanedinitrile derivatives **5a-c** (1 mmol) in absolute EtOH (20 mL) and pipredine (0.1 mL) were heated under reflux for 3h. The precipitated product was filtered off, washed with EtOH and then dried. Recrystallization from DMF/EtOH afforded yellow solid of the corresponding products **9a-c**.

9a: Yield (77%), mp 205-206 ºC; IR (KBr) υ 3310 (NH), 3280 and 3100 (NH_2), 2210 (C≡N), 1720 (C=O), 1665 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.77 (t, 3H, CH_3, J = 6.9 Hz), 3.85 (q, 2H, CH_2, J = 6.9 Hz), 4.30 (d, 1H, CH, J = 6 Hz), 5.28 (d, 1H, CH, J = 6 Hz), 6.75 (s, br., 2H, D_2O-exchangeable NH_2), 7.32-7.45 (m, 10H, ArH's), 10.55 (s, br., 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{24}H_{20}O_3N_4$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.85; H, 4.85; N, 13.53%.

9b: Yield (75%), mp 210-211 ºC; IR (KBr) υ 3295 (NH), 3215 and 3125 (NH_2), 2220 (C≡N), 1730 (C=O), 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{22}O_4N_4$; C, 67.86, H, 5.01; N, 12.66. Found: C, 67.89; H, 5.05; N, 12.68%.

9c: Yield (80%), mp 220-221 ºC; IR (KBr) υ 3355 (NH), 3220 and 3110 (NH_2), 2195 (C≡N), 1715 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.74 (t, 3H, CH_3, J = 6.9 Hz), 3.84 (q, 2H, CH_2, J = 6.9 Hz), 4.25 (d, 1H, CH, J = 6 Hz), 5.25 (d, 1H, CH, J= 6Hz), 6.88 (s, br., 2H, D_2O-exchangeable NH_2), 7.28-7.47(m, 9H, ArH's), 10.50 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 448 (18.2%), 447 (M^+, 5.5%), 446 (57.1%). Anal. Calcd for $C_{24}H_{19}O_3N_4Cl$: C, 64.50; H, 4.29; N, 12.54; Cl, 7.93. Found: C, 64.46; H, 4.32; N, 12.52; Cl, 7.88%.

Ethyl 7-amino-6-(4-chlorophenyl)-3-phenyl-1,2-dihydro-oxopyrazolo[3,4-b]pyrido[1,2-f]pyrimidine-4-carboxylate (14).

To a solution of pyridopyridine **9c** (1 mmol) in EtOH (15 mL), hydrazine hydrate (80%, 0.1 mL, 1 mmol) was added and the reaction mixture was refluxed for 4 h, then left to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallization from DMF/EtOH afforded yellowisch white solid of **14** in 58% yield; mp 260-261 ºC; IR (KBr) υ 3325 (NH), 3215 and 3040 (NH_2), 1703 (C=O), 1659 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.77 (t, 3H, CH_3, J = 6.9 Hz), 3.88 (q, 2H, CH_2, J = 6.9 Hz), 6.15 (s, br., 2H, D_2O-exchangeable NH_2), 7.31-7.49 (m, 10H, ArH's), 9.35 (s, br., 1H,

D_2O-exchangeable NH). Anal. Calcd for $C_{24}H_{18}O_3N_5Cl$: C, 62.68; H, 3.95; N, 15.23. Found: C, 62.63; H, 3.99; N, 15.21%.

Synthesis of ethyl 1,2-dihydro-2-oxo-4-phenyl-6-(substituted styryl)pyrimidine-5-carboxylate 16a-c

General procedure:

A mixture of the appropriate aromatic aldehyde **14a-c** (10 mmol), pyrimidine **1** (2.58 g, 10 mmol) and zinc chloride (1 mmol) was heated at 100º C with constant stirring for 1h. The mixture was cooled to rt and treated with a solution of an aqueous EtOH (1%). The solid product so formed was filtered off and dried. Recrystallizations from DMF/ EtOH afforded **16a-c**.

16a: Yellowisch white solid; yield (70%), mp 250-251 ºC; IR (KBr) υ 3215 (NH), 1715 (C=O), 1650 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_3N_2$: C, 72.82; H, 5.24; N, 8.09. Found: C, 70.83; H, 5.25; N, 7.96%.

16b: Yellowisch white solid, yield (68%), mp 240-241 ºC.; IR (KBr) υ: 3220 (NH), 717 (C=O), 1650 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_4N_2$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.26; H, 5.30; N, 7.43%.

16c: Yellowisch white solid, yield (73%), mp 210-211 ºC; yield (78%); IR (KBr) υ 3215 (NH), 1715 (C=O), 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, 3H, CH_3, J = 7.2 Hz), 4.05 (q, 2H, CH_2, J = 7.2 Hz), 7.25 (d, 1H, CH, J = 16 Hz), 7.39 (d, 1H, CH, J= 16 Hz), 7.50-7.70 (m, 9H, ArH's), 12.32 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{21}H_{17}O_3N_2Cl$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.19; H, 4.52; N, 7.38%.

Reaction of pyrimidine 16c with hydrazine derivatives.

General procedure

To a solution of pyrimidine **16c** (0.76 g, 2 mmol) in EtOH (10 mL), hydrazine hydrate (80%, 0.2 mL, 2 mmol) or phenylhydrazine (0.216 g, 2 mmol) was added. The reaction mixture was refluxed for 4 h, then allowed to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallization from DMF afforded yellowisch white solid of **19** or **22**, respectively.

6-Amino-7-(4-chlorophenyl)-4-phenyl-1H,6H-pyrido[4,3-d]- pyrimidine-2,5-dione (19).

yield (56%); mp>300 ºC; IR (KBr) υ 3350 (NH), 3240-3105 (NH_2), 1697 (C=O), 1675 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.59 (s, br., 2H, D_2O-exchangeable NH_2), 6.72-7.32 (m, 10H, ArH's), 11.35 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{19}H_{13}O_2N_4Cl$: C, 62.56; H, 3.59; N, 15.36. Found: C, 62.60; H, 3.56; N, 15.40%.

7-(4-Chlorophenyl)-4-phenyl-6-phenylamino-1H,6H-pyrido[4,3-d]pyrimidine-2,5-dione (22).

yield (58%); mp>300 ºC; IR (KBr) υ 3250 (NH), 3120 (NH), 1685 (C=O), 1640 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.31-7.69 (m, 15H, ArH's), 10.30 (s, br., 1H, D_2O-exchangeable, NH), 11.38 (s, br., 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{25}H_{17}O_2N_4Cl$: C, 68.10; H, 3.89; N, 12.71; Cl, 8.04. Found: C, 68.20; H, 3.84; N, 12.72; Cl, 8.10%.

Reaction between 6-(bromomethyl)-1,2-dihydro-2-oxo-4-phenylpyrimidine-5-carboxylate (23) with pyridine.

To a solution of ethyl 6-(bromomethyl)-1,2-dihydro-2-oxo-4-phenylpyrimidine-5-carboxylate (**23**)[21] (0.338 g, 10 mmol) in dry THF (30 mL), pyridine (0.8 mL, 10 mmol) was added. The mixture was refluxed for 20 min, then left to cool to RT. The heavy solid product was filtered off, washed with Et_2O and dried to afford white solid of pyridinium salt **24** in 95% yield, mp 210-211 ºC; IR (KBr) υ 3275 (NH), 1715 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.68 (t, 3H, CH_3, J = 6.9 Hz), 3.79 (q, 2H, CH_2, J = 6.9 Hz), 4.22 (s, 2H, CH_2), 7.31-7.68 (m, 10H, ArH's), 11.32 (s, br., 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{19}H_{18}O_3N_3Br$: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.88; H, 4.32; N, 10.10%.

8-Bromo-6-(4-chlorophenyl)-4-phenyl-1H,6H-pyrimido[4,5-d] pyridazine-2,5-dione (26)

To a stirred solution of pyridinium salt **24** (0.427 g, 1 mmol) in EtOH (20 mL) was added the diazonium salt of 4-chloroaniline [prepared by diazotizing 4-chloroaniline (0.126 g,1 mmol) in hydrochloric acid (6M, 0.6 mL) with sodium nitrite solution (0.069 g, 1 mmol) in water (0.5 mL)]. The addition of the diazonium salt was carried out with rapid stirring over a period of 30 min. the reaction mixture was stirred for further 1h at 0-5 ºC. The resulting solid product was collected by filteration, washed with water followed by EtOH and then dried. Recrystallization from DMF afforded yellowish white solid of pyrimidopyridazine **26** in 75% yield, mp 305-306 ºC; IR (KBr) υ 3290 (NH), 1674 (C=O), 1636 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.32-9.47 (m, 9H, ArH's), 8.85 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 430 (M^+, 4.3%), 429(24.2%), 428(14.8%), 427(44%), 426(9.0%), 79 (26.1%), 78(100%), 77(20.8%). Anal. Calcd for $C_{18}H_{10}O_2N_4ClBr$: C, 50.32; H, 2.35; N, 13.04; Cl, 8.25. Found: C, 50.39; H, 2.36; N, 13.10; Cl, 8.30%.

Synthesis of ethyl 6-(5-amino-4-cyano-3-aryl-2,3-dihydrothiophen-2-yl)-2-oxo-4-phenyl- 1,2-dihydro-pyrimidine-5-carboxylate 29a,b

General procedure

To a solution of pyridinium salt **24** (0.427 g, 1 mmol) and the appropriate 2-cyano-2-arylmethylene thioacetamide **27a,b** (1 mmol) in absolute EtOH (20 mL), triethylamine (0.1 mL) was added and the reaction mixture was refluxed for 3h, then left to cool. The precipitated products were filtered off, washed with water and then dried. Recrystallization from DMF afforded yellow solid of thiazole derivatives **29a,b**.

29a: Yield (63%), mp 260-261 ºC; IR (KBr) υ 3395 (NH), 3194-3310 (NH_2), 2175 (C≡N), 1705 (C=O), 1666 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.69 (t, 3H, CH_3, J = 6.9 Hz), 3.74 (q, 2H, CH_2, J = 6.9 Hz), 3.80 (s, 3H, CH_3), 4.73 (d, 1H, CH, J= 3.9 Hz), 4.9 (d, 1H, CH, J= 3.9 Hz), 6.92 (s, br., 2H, D_2O-exchangeable NH_2), 6.91-7.55 (m, 9H, ArH's), 12.6 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 474 (M^+, 4.4%), 473(5.3%), 472(5.7%), 442(31.6%), 441(100.0%). Anal. Calcd for $C_{25}H_{22}O_4N_4S$: C, 63.28, H; 4.67, N: 11.81. Found: C, 63.26; H, 4.70; N, 11.89%.

29b: Yield (70%), mp 265-266 ºC; IR (KBr) υ 3380 (NH), 3220-3175 (NH_2), 2176 (C≡N), 1710 (C=O), 1670 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.64 (t, 3H, CH_3, J = 7.0 Hz), 3.80 (q, 2H, CH_2, J = 7.0 Hz), 4.74 (d, 1H, CH, *J* = 2.7 Hz), 4.94 (d, 1H, CH, *J* = 2.7 Hz), 7.15 (s, br., 2H, D_2O-exchangeable NH_2), 7.42-7.55 (m, 9H, ArH's), 12.7 (s, br., 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{24}H_{19}O_3N_4SCl$: C, 60.19; H, 4.00; N, 11.70. Found: C, 60.22; H, 4.10; N: 11.72%.

ANTIMICROBIAL ACTIVITY

Compounds **9b,c**, **14** and **26** 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, *Staphylcoccus 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 depicted in Table 1.

Table 1. Antimicrobial activity of compounds 9b, 9c, 14 and 26

Micro-organism/IZD (cm)*

Sample	**9b**			**9c**			**14**			**26**			**Standard mg/mL**		
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	+++	+++	++
(PI)	++	+	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)	++	++	0	++	++	0	++	++	0	++	++	++	++	++	++
(PA)	0	0	0	0	0	0	0	0	0	0	0	0	+++	+++	++
(BS)	0	0	0	++	++	0	0	0	0	++	++	++	+++	+++	++
(EC)	+	0	0	0	0	0	0	0	0	++	++	++	++	++	++

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

The test results revealed that all compounds exhibited a moderate activity against *Staphylcoccus aureus* (**SA)** at concentrations of 5 and 2.5 mg/mL and showed almost no activity at concentration of 1 mg/mL except compound **26** which showed a moderate activity**.** Compound **26** exhibited also a moderate activity against *Escherichia coli* **(EC)** at all concentrations. Compound **9c** exhibited only a moderate activity against *Bacillus subtilis* (**BS**) at concentrations of 5 and 2.5 mg/mL, respectively. All compounds exhibited

almost no activity against *Aspergillus fumigatus* (**AF)**, *Penicillium italicum* **(PI)**, *Syncephalastrum racemosum* (**SR)**, *Candida albicans* **(CA)** and *Pseudomonas aeruginosa* **(PA)** except compound **9b** which exhibited a moderate activity against *Aspergillus fumigatus* (**AF)** at a concentration of 5 mg/mL.

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