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A CONVENIENT ROUTE TO NEW PYRROLO[1,2-*c*]PYRIMIDONE, THIAZOLO[3,4-*c*]PYRIMIDONE AND PYRIMIDO[4,5-*d*]PYRIDAZINE DERIVATIVES

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Abstract – The utility of versatile, readily accessible ethyl 6-bromomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**) and ethyl 6-bromomethyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**4**) in the synthesis of some new pyrimidine, pyrimido[4,5-*d*]pyridazine, pyrrolo[1,2-*c*]pyrimidone and thiazolo[3,4-*c*]pyrimidone derivatives is reported.

INTRODUCTION

Multifunctionalized dihydropyrimidine derivatives represent heterocyclic systems of remarkable pharmacological efficiency. A broad range of medicinal effects, including antiviral, antitumor, antibacterial, and antiinflammatory activities has been ascribed to these partly reduced pyrimidine derivatives.[1] On the other hand, several pyrrolo[l,2-*c*]pyrimidine compounds have been found to be useful as pharmaceutically interesting compounds.[2] Also, pyrimido[4,5-*d*]pyrimidine derivatives are useful as bronchodilators[3] and are used as antifungal[4] and for treatment of tumor diseases.[5]

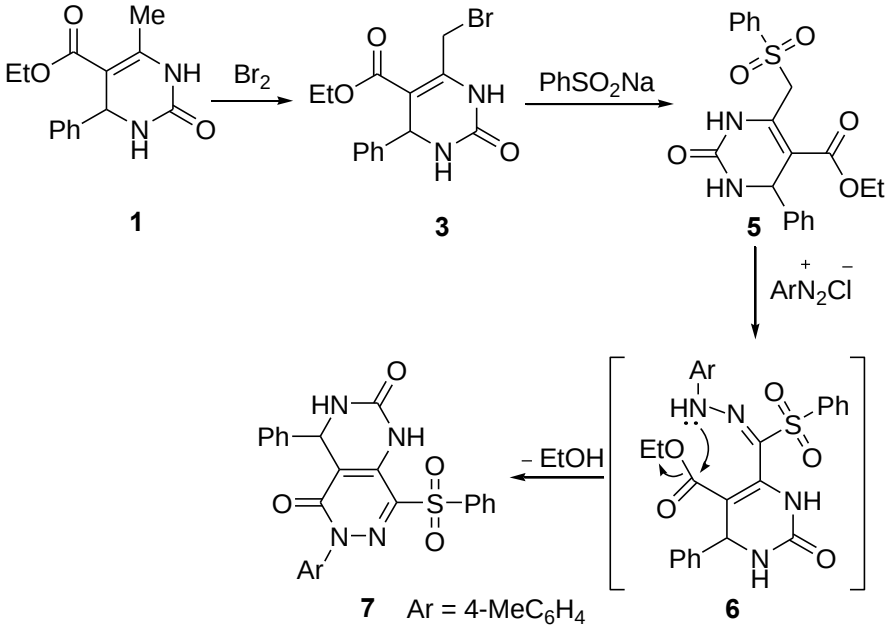
Encouraged by these findings and in continuation of our previous work aimed at the synthesis of a variety of heterocyclic systems for biological and pharmacological evaluation,[6-18] we have found that 6-bromomethylpyrimidine derivatives **3**[19] and **4** are a versatile, readily accessible building blocks for the synthesis of new pyrrolo[1,2-*c*]pyrimidone, thiazolo[3,4-*c*]pyrimidone and pyrimido[4,5-*d*]pyridazine derivatives of expected biological importance.

RESULTS AND DISCUSSION

The versatile synthons ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**)[19] and ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**4**), were obtained

from bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**),[20] and ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**2**)[21] in acetic acid.

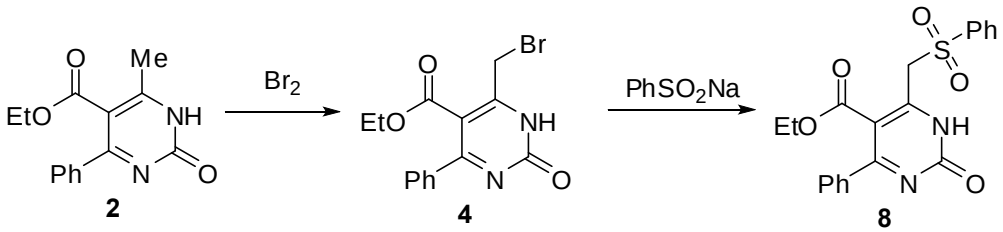
Treatment of 6-bromomethylpyrimidine **3** with sodium benzenesulfinate afforded ethyl 2-oxo-4-phenyl-6-(phenylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5**) (Scheme 1). The IR spectrum of the pyrimidine derivative **5** exhibited absorption bands at 1647, 1705, 3113 and 3337 cm^{-1} corresponding to two carbonyl groups, and two imino functions, respectively. Its ^1H NMR spectrum revealed a triplet signal at δ 1.00 (J = 7.5 Hz) due to CH_3 protons, a quartet signal at δ 3.73 (J = 7.5 Hz) due to CH_2 protons, two singlet signal at δ 4.94 and 5.12 due to CH_2 and CH protons, respectively. It showed also two D_2O-exchangeable signals at δ 7.80 and 9.10 due to two NH protons, in addition to an aromatic multiplet in the region 7.22-7.73. Compound **5** couples smoothly with diazotized 4-methylaniline to afford 4-phenyl-8-(phenylsulfonyl)-6-(*p*-tolyl)-3,4-dihydropyrimido-[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**7**) (Scheme 1). The IR spectrum of pyrimido[4,5-*d*]pyridazine **7** showed absorption bands at 1663, 1720, 3105 and 3387 cm^{-1} corresponding to two carbonyl groups and two imino functions, respectively. Its ^1H NMR spectrum revealed the absence of CH_3 and CH_2 protons of ethoxycarbonyl group and showed signals at δ 5.43 due to CH proton. It showed also two D_2O-exchangeable signals at δ 7.25 and 8.32 due to two NH protons, in addition to an aromatic multiplet in the region 7.31-8.07.



Scheme 1

Bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**2**) in acetic acid, afforded the corresponding 6-bromomethyl derivative **4** (Scheme 2). Treatment of the latter compound with sodium benzenesulfinate afforded the corresponding ethyl 2-oxo-4-phenyl-6-(phenylsulfonylmethyl) -1,2-dihydropyrimidine-5-carboxylate (**8**) (Scheme 2). The IR spectrum of the product **8** revealed absorption bands at 1647, 1705 and 3337 cm^{-1} corresponding to two carbonyl groups, and two imino

functions, respectively. Its ^{1}H NMR spectrum showed a triplet signal at δ 0.99 (J = 7.5 Hz) due to CH_3 protons and a quartet signal at δ 3.74 (J = 7.5 Hz) due to CH_2 protons, and a singlet signal at δ 4.83 due to CH_2 protons. It showed also D_2O-exchangeable signal at δ 9.1 due to NH proton, in addition to an aromatic multiplet in the region 7.24-7.73



Scheme 2

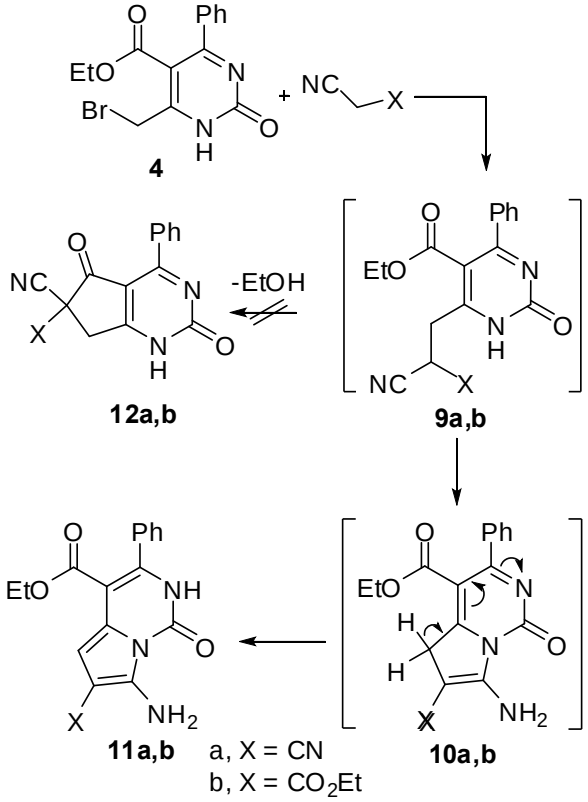
Treatment of 6-bromomethylpyrimidine **4** with malononitrile and with ethyl cyanoacetate afforded the corresponding ethyl 7-amino-6-cyano-1,2-dihydro-1-oxo-3-phenylpyrrolo[1,2-*c*]pyrimidine-4-carboxylate (**11a**) and 4,6-diethyl 7-amino-1,2-dihydro-1-oxo-3-phenylpyrrolo[1,2-*c*]pyrimidine-4,6-dicarboxylate (**11b**), respectively (Scheme 3)**.** The IR spectrum of compound **11b**, taken as a typical example of the prepared compounds, exhibited absorption bands at 1675, 1715, 1720, 3280-3320 and 3445 cm^{-1} corresponding to three carbonyl groups, amino and imino functions, respectively. Its ^{1}H NMR spectrum revealed signals at δ 0.83, 1.27, 3.93, 4.19 and 6.43 due to two ethoxycarbonyl and CH protons, respectively. It showed also D_2O-exchangeable signals at δ 6.84 and 10.92 corresponding to NH_2 and NH protons, respectively, in addition to an aromatic multiplet in the region δ 7.34-7.44. Its mass spectrum revealed a molecular ion peak at *m/z* 369.

Reaction of the 6-bromomethyl derivative **4** with thiosemicarbazide afforded ethyl 3-hydrazono-5,6-dihydro-5-oxo-7-phenyl-3*H*-thiazolo[3,4-*c*]pyrimidine-8-carboxylate (**14**) (Scheme 4). The IR spectrum of the product **14** revealed absorption bands at 1675, 1735 and 3225-3195 corresponding to two carbonyl groups, amino and imino functions, respectively. Its ^{1}H NMR spectrum showed a triplet signal at δ 0.9 (J = 7.2 Hz) due to CH_3 protons, a quartet signal at δ 4.03 (J = 7.2 Hz) due to CH_2 protons, two D_2O-exchangeable signals at δ 8.66 and 12.05 due NH_2 and NH protons, respectively, in addition to an aromatic multiplet in the region δ 7.49-7.53.

The above reaction is assumed to proceed *via* nucleophilic substitution of bromine atom in compound **4** by thiosemicarbazide moiety to afford the acyclic intermediate **13** which underwent intramolecular cyclocondensation through elimination of ammonia molecule to afford the final product **14** as shown in Scheme 4.

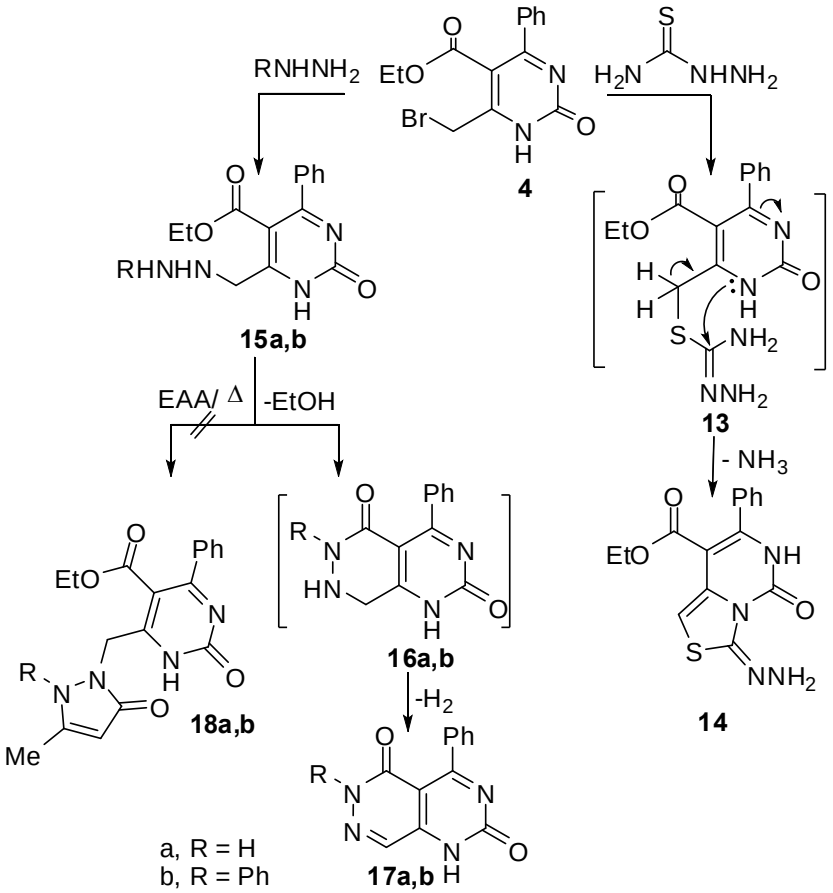
Similarly, nucleophilic substitution reaction of bromine atom in 6-bromomethyl derivative **4** with hydrazine hydrate and with phenylhydrazine, afforded ethyl 6-hydrazinomethyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate **(15a)** and ethyl 2-oxo-4-phenyl-6-((2-phenylhydrazinyl)methyl)-1,2-

dihydropyrimidine-5-carboxylate (**15b**), respectively (Scheme 4). The IR spectrum of compound **15b**, taken as a typical example of the prepared compounds, revealed absorption bands at 1670, 1718, 3010, 3120, 3285 cm^{-1} corresponding to two carbonyl groups, and three imino functions, respectively. Its ^1H NMR spectrum showed a triplet signal at δ 0.86 (J = 7.2 Hz) due to CH_3 protons, a singlet signal at δ 3.35 (J = 7.2 Hz) due to CH_2 protons, a quartet signal at δ 3.95 due to CH_2 protons and three D_2O-exchangeable signal at δ 7.84, 11.61, 11.90 corresponding to three NH protons, in addition to an aromatic multiplet in the region δ 6.91-7.55.



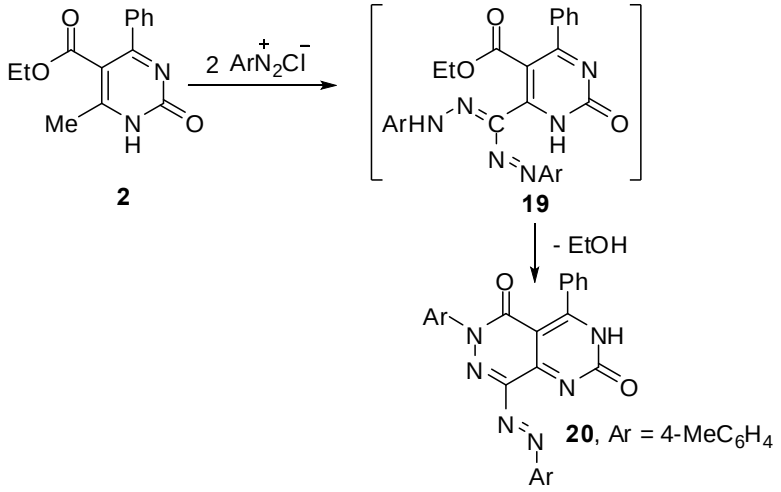
Scheme 3

Heating of compounds **15a** and **15b** in ethyl acetoacetate led to the formation of products identified as 4-phenylpyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**17a**) and 4,6-diphenyl-1*H*-pyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)dione (**17b**), respectively, instead of the expected pyrazolone structures **18a** and **18b**, respectively (Scheme 4). The IR spectrum of compound **17a**, revealed absorption bands at 1659, 1690, 3040 and 3220 cm^{-1} corresponding to two carbonyl, and two imino functions, respectively. Its ^1H NMR spectrum revealed the disappearance of the signal corresponding to CH_3 and CH_2 protons of ethoxy group and showed two D_2O-exchangeable signals at δ 7.94 and 12.87 corresponding to two NH protons, in addition to an aromatic multiplet in the region δ 7.38-7.56. Compounds **17a** and **17b** are assumed to be formed through intramolecular cyclization of compounds **15a** and **15b** *via* loss of EtOH molecule under the reaction conditions (a high boiling solvent) followed by dehydrogenation to afford the final products **17a,b** as shown in Scheme 4.



Scheme 4

The 1,2-dihydropyrimidine **2** couples smoothly with 4-methylbenzene diazonium chloride to afford the corresponding 6-(4-methylphenyl)-8-(4-methylphenylazo)-4-phenyl-1*H*-pyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**20**) (Scheme 5). The IR spectrum of compound **20** exhibited absorption bands at 1650, 1675 and 3245 cm^{-1} corresponding to two carbonyl groups and an imino function, respectively. Its ^1H NMR spectrum revealed a singlet signal at δ 2.35 due to CH_3 protons and D_2O-exchangeable signal at δ 10.72 due to NH proton, in addition to an aromatic multiplet in the region 7.31-7.66. Also, its mass spectrum revealed a molecular ion peak at *m/z* 448.



Scheme 5

The above reaction is assumed to take place by coupling of the diazonium salt at an active methyl group in compound **2** and formation of the formazan-type[22,23] intermediate **19** which undergwent intramolecular cyclocondensation *via* loss of ethanol molecule, under the reaction conditions, to afford the final product **20** as shown in Scheme 5.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 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 and ^{13}C 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 recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**),[20] ethyl 6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**2**)[21] and ethyl 6-bromomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**)[19] were prepared following the literature procedure.

Ethyl 6-bromomethyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (4).

To a solution of the 1,2-dihydropyrimidine **2** (2.58 g, 10 mmol) in acetic acid (20 mL), bromine (0.52 mL, 10 mmol) in acetic acid (12 mL) was added portion-wise at 40-50 ºC for 1 h, then the resulting mixture was poured onto cold water. The precipitated solid was collected by filtration, washed with water, dried and finally crystallized from EtOH afforded white crystals (72% yield), mp 170-171 ºC (EtOH); IR (KBr) ν 3280 (NH), 1718 (C=O), 1665 (C=O) cm^{-1}; ^{1}H NMR (CDC1$_3$) δ 0.87 (t, 3H, CH_3, J = 6.9 Hz), 4.0 (q, 2H, CH_2, J = 6.9 Hz), 4.54 (s, 2H, CH_2), 7.40-7.57 (m, 5H, ArH), 9.6 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 338 (12.9), 337 (6.4), 336 (7.2), 291 (14.3), 257 (100.0), 229 (83.8), 184 (12.9), 140 (10.3), 104 (39.4). Anal. Calcd for $C_{14}H_{13}O_3N_2Br$: C, 49.87; H, 3.89; N, 8.31. Found: C, 49.90; H, 3.86; N, 8.28%.

Synthesis of 6-(phenylsulfonylmethyl)pyrimidine 5 and 8.

General procedure

A solution of the appropriate 6-bromomethylpyrimidine derivatives **3** or **4** (1 mmol) in EtOH 10 mL and sodium benzenesulfinate (0.164 g, 1 mmol) was heated under reflux for 1 h then left to cool. The resulting mixture was diluted with water (3 mL). The solid precipitate was filtered off, washed with water and dried. Recrystallization from the EtOH give the corresponding 6-(phenylsulfonylmethyl)pyrimidine derivatives **5** and **8**, respectively,

Ethyl 2-oxo-4-phenyl-6-(phenylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5). Yield (71%), mp 234-5 ºC; IR (KBr) ν 3337 (NH), 3113 (NH), 1705 (C=O), 1647 (C=O) cm^{-1}; ^{1}H NMR

(DMSO-d_6) δ 1.00 (t, 3H, CH_3, J = 7.5 *Hz*), 3.73 (q, 2H, CH_2, J = 7.5 Hz), 4.94 (s, 2H, CH_2), 5.12 (d, 1H, CH, J = 2.7 Hz), 7.22-7.73 (m, 10H, ArH's), 7.80 (s, 1H, D_2O-exchangeable, NH), 9.10 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ 13.68, 54.06, 55.71, 59.73, 104.32, 126.24, 127.51, 128.13, 128.37, 128.98, 133.97, 137.81, 138.25, 143.72, 151.74, 164.09. Anal. Calcd for $C_{20}H_{20}O_5N_2S$: C, 59.99; H, 5.03; N, 7.00. Found: C, 59.97; H, 5.00; N, 7.03%.

Ethyl 2-oxo-4-phenyl-6-(phenylsulfonylmethyl)-1,2-dihydropyrimidine-5-carboxylate (8).

Yield (73%), mp 232-3 ºC; IR (KBr) ν 3337 (NH), 1705 (C=O), 1647 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.99 (t, 3H, CH_3, J = 7.5 Hz), 3.74 (q, 2H, CH_2, J = 7.5 Hz), 4.83 (s, 2H, CH_2), 7.24-7.73 (m, 10H, ArH's), 9.1 (s, 1H, D_2O-exchangeable, NH). MS *m/z* (%) 402 (7.0), 401 (9.4), 400 (4.9), 356 (7.8), 355 (12.3), 141 (10.2), 77 (100.0). Anal. Calcd for $C_{20}H_{18}O_5N_2S$: C, 60.29; H, 4.55; N, 7.03. Found: C, 60.32; H, 4.58; N, 7.05%.

4-Phenyl-8-(phenylsulfonyl)-6-(p-tolyl)-3,4-dihydropyrimido[4,5-d]pyridazine-2,5-(1H,6H)-dione (7).

To a cold solution of the pyrimidine derivative **5** (0.4 g, 1 mmol) in pyridine (5 mL) was added an equimolar amount of 4-methylbenzene diazonium chloride [prepared by diazotizing 4-methylaniline (0.107 g, 1 mmol) in hydrochloric acid (6 M, 0.3 mL) with sodium nitrite solution (0.07 g, 1 mmol, in 1 mL water). The addition was carried out portion-wise with stirring at 0-5 ºC 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. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from EtOH to afford the 4-phenyl-8-(phenylsulfonyl)-6-(*p*-tolyl)-3,4-dihydropyrimido[4,5-*d*]pyridazine-2,5-(1*H*,6*H*)-dione (**7**) in 75 %yield. mp 244-5 ºC; IR (KBr) ν 3387 (NH), 3213 (NH), 1720 (C=O), 1663 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 5.43 (d, 1H, CH, J = 2.7 Hz), 7.25 (s, 1H, D_2O-exchangeable, NH), 7.31-8.07 (m, 14H, ArH's), 8.32 (s, 1H, D_2O-exchangeable, NH). Anal. Calcd for $C_{25}H_{20}O_4N_4S$: C, 63.55; H, 4.27; N, 11.86. Found: C, 63.57; H, 4.30; N, 11.88%.

Reaction of 6-bromomethylpyrimidine derivative 4 with malononitrile and ethyl cyanoacetate.

General procedure

To a solution of **4** (0.34 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) or ethyl cyanoacetate (0.113 mL, 1 mmol) in EtOH (20 mL) was added few drops of piperidine and the reaction mixture was refluxed for 4 h then left to cool. The formed solid product was collected by filtration, washed with EtOH and purified by crystallization from the appropriate solvent to afford the corresponding pyrrolo[1,2-*c*]pyrimidine derivatives **11a** and **11b**, respectively.

Ethyl 7-amino-6-cyano-1,2-dihydro-1-oxo-3-phenylpyrrolo[1,2-c]pyrimidine-4-carboxylate (11a). Yield (79%), mp > 300 ^{o}C (DMF); IR (KBr) ν 3441 (NH), 3317-3240 (NH) and NH_2, 2120 (C≡N), 1728 (C=O), 1697 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, 3H, CH_3, J = 7.2 Hz), 3.94 (q, 2H, CH_2, J = 7.2 Hz), 6.38 (s,1H, CH), 7.33-7.46 (m, 5H, ArH), 7.04 (s, 2H, D_2O-exchangeable NH_2), 11.06 (s,1H,

D_2O-exchangeable NH); ^{13}C NMR (DMSO-d_6): δ 14.60, 61.12, 102.53,102.78, 116.38, 120.78, 120.82, 127.79, 128.35, 128.45, 130.57, 133.33, 147.90, 152.36, 163.81; MS *m/z* (%) 325 (2.3), 323 (73.7), 322 (M^+, 100.0), 321 (6.2), 295 (12.0). Anal. Calcd for $C_{17}H_{14}O_3N_4$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.40; H, 4.36; N, 17.35%.

Diethyl 7-amino-1,2-dihydro-1-oxo-3-phenylpyrrolo[1,2-c]pyrimidine-4,6-carboxylate (11b). Yield (61%), mp 225-226 °C (EtOH/ DMF); IR (KBr) ν 3445 (NH), 3320-3280 (NH) and NH_2, 1720 (C=O), 1715 (C=O), 1675 (C=O cm^{-1}; ^1H NMR (DMSO- d_6) δ 0.83 (t, 3H, CH_3, J = 6.9 Hz), 1.27 (t, 3H, CH_3, J = 6.9 Hz), 3.93 (q, 2H, CH_2, J = 6.9 Hz), 4.19 (q, 2H, CH_2, J = 6.9 Hz), 6.43 (s, 1H, CH), 6.84 (s, 2H, D_2O-exchangeable NH_2), 7.34-7.44 (m, 5H, ArH), 10.92 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (DMSO-d_6): δ 13.29, 14.46, 58.97, 60.33, 94.20, 101.67, 103.33, 120.02, 127.96, 128.47, 129.04, 133.55, 137.51, 144.85, 148.32, 164.19, 164.59; MS *m/z* (%) 371 (4.3), 370 (21.3), 369 (M^+, 100), 323 (62.1), 297 (1.5), 266 (73.2), 104 (17.6). Anal. Calcd for $C_{19}H_{19}O_5N_3$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.76; H, 5.15; N, 11.41%.

Ethyl 3-hydrazono-5,6-dihydro-5-oxo-7-phenyl-3H-thiazolo[3,4-c]pyrimidine-8-carboxylate (14).

To a solution of **4** (0.337 g, 1 mmol) in EtOH (20 mL), and thiosemicarbazide (0.92 g, 1 mmol) was added and the reaction mixture was refluxed for 4 h, and then allowed to cool. The solid product was collected by filtration, washed with EtOH and crystallized from DMF/EtOH to afford **14** in 63% yield, mp 285-287 °C (DMF); IR (KBr) ν 3380 (NH), 3225-3195 (NH_2), 1735 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6) δ 0.90 (t, 3H, CH_3, J = 7.2 Hz), 4.03 (q, 2H, CH_2, J = 7.2 Hz), 7.49-7.53 (m, 5H, ArH), 8.12 (s, 1H, CH), 8.66 (s, 1H, D_2O-exchangeable NH), 12.05 (s, 2H, D_2O-exchangeable NH_2); ^{13}C NMR (DMSO-d_6): δ 13.27, 61.58, 109.45, 120.87, 127.42, 128.28, 129.61, 130.36, 138.08, 154.63, 165.01, 172.40, 179.14. Anal. Calcd for $C_{15}H_{14}O_3N_4S$: C, 54.53; H, 4.27; N, 16.96. Found: C, 54.56; H, 4.32; N, 16.87%.

Reaction of 4 with hydrazine derivatives.

General procedure:

To a solution of **4** (0.674 g, 2 mmol) in EtOH (20 mL), and hydrazine hydrate (80%, 0.2 mL, 2 mmol) or with phenylhydrazine (0.216 g, 2 mmol) was added and the reaction mixture was refluxed for 4 h, and then allowed to cool. The formed solid product was collected by filtration, washed with EtOH and crystallised from EtOH/DMF to afford compounds **15a** and **15b**, respectively.

Ethyl 6-hydrazinomethyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (15a). Yield (71%), mp 235-236 °C (EtOH/DMF); IR (KBr) ν 3320 (NH), 3275 (NH), 3100 (NH_2), 1725 (C=O), 1655 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6) δ 0.85 (t, 3H, CH_3, J = 6.9 Hz), 3.8 (q, 2H, CH_2, J = 6.9 Hz), 4.07 (s, 2H, CH_2), 7.19-7.45 (m, 5H, PhH), 8.78 (s, 2H, D_2O-exchangeable NH_2), 10.87 (s, 1H, D_2O-exchangeable NH), 11.72 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 288 (M^+, 18.1), 272 (100.0), 244 (11.0), 180

(12.9), 141 (14.7), 77 (48.9). Anal. Calcd for $C_{14}H_{16}O_3N_4$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.28; H, 5.57; N, 19.39%.

Ethyl 2-oxo-4-phenyl-6-((2-phenylhydrazinyl)methyl)-1,2-dihydropyrimidine-5-carboxylate (15b). Yield (79%), mp 220-221 ^oC (EtOH); IR (KBr) ν 3285 (NH), 3120 (NH), 1718 (C=O), 1670 (C=O). cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.86 (t, 3H, CH_3, J = 7.2 Hz), 3.35 (s, 2H, CH_2), 3.95 (q, 2H, CH_2, J = 7.2 Hz), 6.91-7.55 (m, 10H, Ar H), 7.84 (s, 1H, D_2O- exchangeable NH), 11.61 (s, 1H, D_2O-exchangeable NH), 11.9 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (DMSO-d_6): δ 13.25, 40.33, 52.64, 61.02, 88.95, 107.33, 113.82, 121.67, 127.54, 128.18, 129.07, 130.62, 132.16, 143.14, 155.61, 165.96; MS *m/z* (%) 364 (M^+, 5.2), 363 (32.3), 315 (47.1), 229 (60.9), 171 (16.5), 77 (100.0). Anal. Calcd for $C_{20}H_{20}O_3N_4$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.87; H, 5.48; N, 15.40%.

Synthesis of pyrimido[4,5-d]pyridazine derivatives 17a and 17b.

General procedure:

A solution of **15a** or **15b** (0.728 g, 2 mmol) in ethyl acetoacetate (5.0 mL) was refluxed for 3h, then left to cool to rt. The precipitated solid was collected by filtration, washed with EtOH and crystallized from DMF/EtOH to afford **17a** and **17b**, respectively.

4-Phenylpyrimido[4,5-d]pyridazine-2,5-(1H,6H)-dione (17a). Yield (84%), mp >300 ^oC; IR (KBr) ν 3220 (NH), 3040 (NH), 1690 (C=O), 1659 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6) δ 7.38-7.56 (m, 6H, ArH), 7.94 (s, 1H, D_2O-exchangeable NH), 12.87 (s, 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{12}H_8O_2N_4$: C, 60.00; H, 3.36; N, 23.32. Found: C, 60.09; H, 3.32; N, 23.30%.

4,6-Diphenyl-1H-pyrimido[4,5-d]pyridazine-2,5-(1H,6H)-dione (17b). Yield (79%), mp 295-297 ^oC (DMF); IR (KBr) ν 3220 (NH), 1695 (C=O), 1670 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6) δ 7.38-7.85 (m, 10H, ArH), 8.14 (s, 1H, CH), 12.74 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (DMSO-d_6): δ 106.53, 121.56, 125.95, 127.16, 127.95, 128.19, 128.52, 128.65, 129.07, 129.85, 137.83, 141.21, 155.78, 164.72; MS *m/z* (%) 316 (M^+, 99.5), 315 (55.6), 156 (28.9), 91 (18.7), 78 (13.9), 77 (100.0). Anal. Calcd for $C_{18}H_{12}O_2N_4$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.32; H, 3.80; N, 17.74%.

6-(4-Methylphenyl)-8-(4-methylphenylazo)-4-phenyl-1H-pyrimido[4,5-d]pyridazine-2,5(1H,6H)-dione (20).

To a cold solution of the pyrimidone **2** (2.85 g, 10 mmol) in ethanol (50 mL) and sodium acetate trihydrate (3 g) was added equimolar amount of 4-methylbenzene diazonium chloride [prepared by diazotizing 4-methylaniline (1.07 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 portion-wise with stirring at 0-5 ºC 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 crystallized from DMF to afford red crystals of **20**. Yield (71%); mp

> 300 °C (DMF); IR (KBr) ν 3245 (NH), 1675 (C=O), 1650 cm^{-1} (C=O) cm^{-1}; ^1H NMR (DMSO- d_6) δ 2.35 (s, 6H, $2CH_3$), 7.31-7.66 (m, 13H, Ar′ H), 10.72 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 448 (M^+, 10.4), 391 (9.5), 345 (23.2), 242 (7.0), 106 (100.0), 101 (2.8), 77 (28.4). Anal. Calcd for $C_{26}H_{20}O_2N_6$: C, 69.63; H, 4.49; N, 18.74. Found: C, 69.59; H, 4.49; N, 18.71%.

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