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CONJUGATE ADDITION REACTIONS OF SOME METHYLIDENE 1-BENZYLPYRIMIDINETRIONE DERIVATIVES

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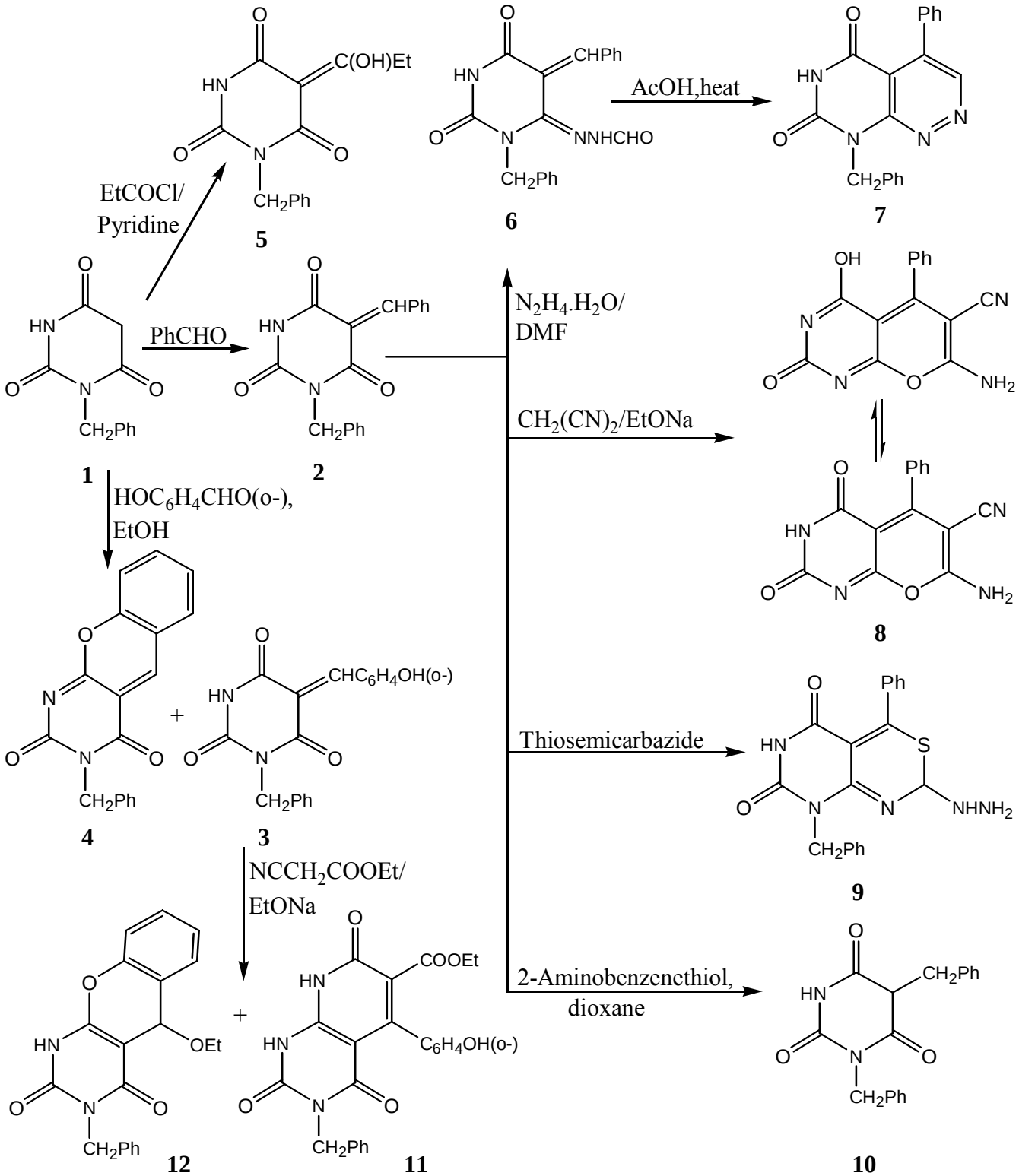
Abstract-1-Benzyl-2,4,6-pyrimidinetrione (**1**) reacts at *C*-5 with aldehydes and the isolated products can easily undergo base-induced transformations by Michael addition. On the contrary,the action of $POCl_3$ or piperidine/AcOH on the title trione afforded pyrimido[4',5':4,5]furo[2,3-*d*]pyrimidine (**16**) and a dimer (**17**), respectively, which in turn, undergo cyclocondensation in Ac_2O.

Several approaches[1-4]have been employed for the synthesis of pyrimidine derivatives, especially for their potential antibacterial properties,[5,6] and as for some recent applications, they have been used as dihydrofolate reductase inhibitors and as antitumor agents.[7-10] Because of our continued interest in the condensation reaction of Michael acceptors with active methylene compounds[11-13] and amines, we expanded this study to cover the reaction of 1-benzyl and\or methylidenepyrimidinetrione derivatives with malononitrile, ethyl cyanoacetate and some amines in order to obtain pyrimidine derivatives of expected biological activities.Various compounds prepared (**3-18**) are outlined in Schemes 1 and 2.

RESULTS AND DISCUSSION

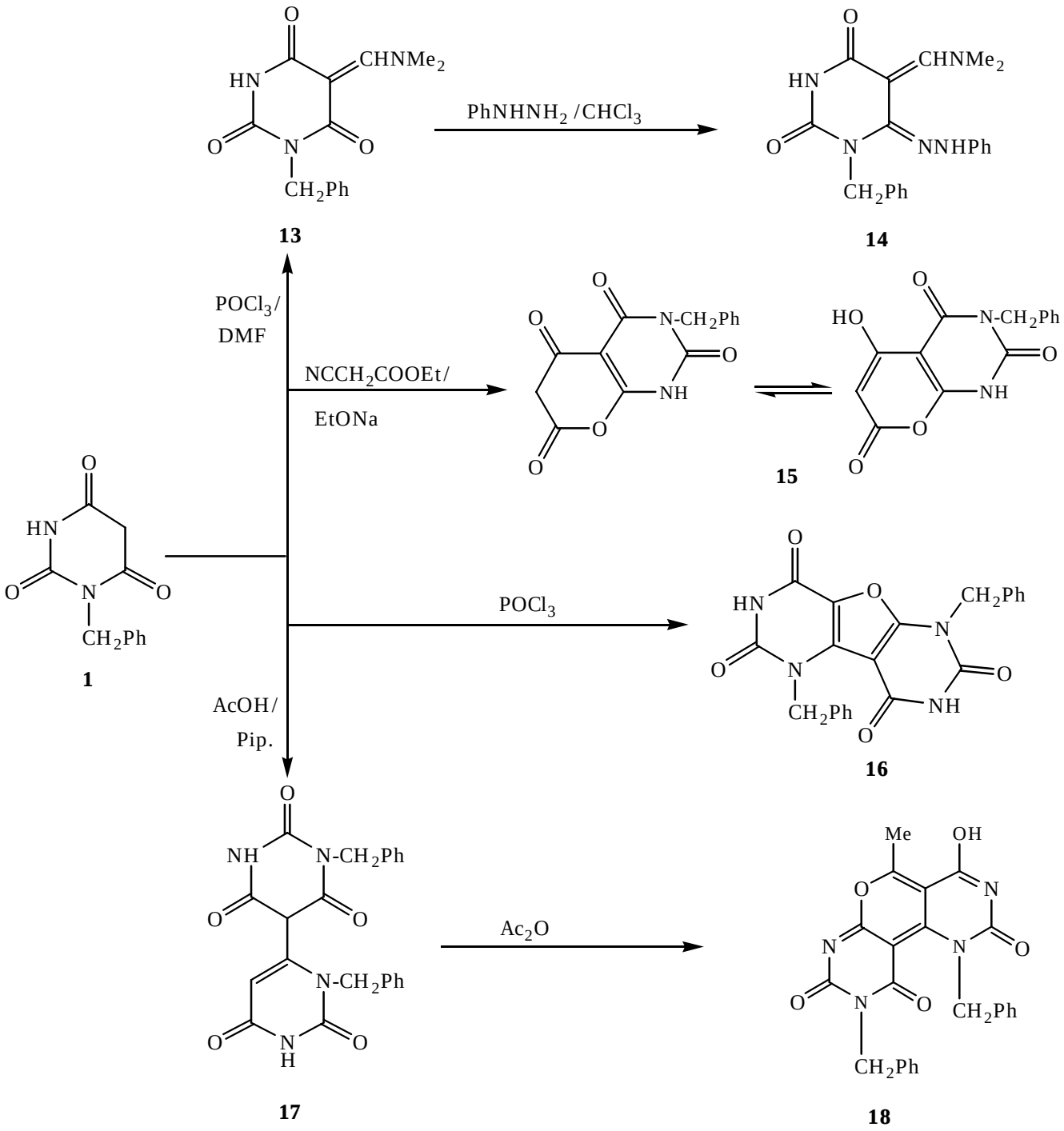
In the present investigation, aryl methylidenepyrimidinetrione derivative (**2**) and (3),[14] obtained from the condensation of 1-benzyl-2,4,6-pyrimidinetrione (**1**) with benzaldehyde and/or salicylaldehyde, are used as starting materials for the syntheses outlined in Scheme 1. While, the hydroxypropylidene derivative (**5**) was synthesized by condensation of propionyl chloride with the benzylpyrimidinetrione (**1)** in the presence of triethylamine.[15] The MS spectrum of **5** revealed the molecular ion and base peak at *m/z* 274.

Thus, reaction of **2** with hydrazine hydrate in dimethylformamide gave the formic hydrazide derivative (**6**), which undergo cyclization on boiling in acetic acid affording the pyrimido[4,5-*c*]-pyridazine derivative (**7**). The proposed structure for derivatives (**6**) and (**7**) was confirmed by ^{1}H NMR spectra. For compound (**6**) two peaks were observed at δ 8.77 of the methylidene group and δ 8.43 of the formyl group, while compound (**7**) showed peak at δ 8.76 of the aromatic pyridazine proton. The reaction of compound (**2**) with malononitrile in ethanol in presence of sodium ethoxide at room temperature[16] led to the formation of 2*H*-pyrano[2,3-*d*]pyrimidine derivatives (**8**) through Michael addition of the malononitrile carbanion to the methyllidene group of **2**, followed by a nucleophilic attack by the carbonyl oxygen on one of the cyano groups, disproportionation and debenzylation. However, pyrimido[4,5-*d*][1,3]thiazinedione derivative (**9**) was obtained by conjugate addition of thiosemicarbazide to the methylidene group[17] of **2**, followed by cyclo-



Scheme 1

condensation with the formation of the oxidized product, therefore, it was impossible to isolate the intermediate dihydro derivative. Another noteworthy result was the conversion of compound (**2**) to 1,5-dibenzyl-2,4,6(1*H*,3*H*,5*H*) pyrimidinetrione (**10**) upon refluxing with 2-aminobenzenethiol in dioxane, implying that under these conditions the primary Michael adduct subsequently undergoes reduction.[18] When benzylpyrimidinetrione (**1**) was allowed to react with salicylaldehyde in boiling ethanol,[14] arylmethyl-



Scheme 2

idene pyrimidine (**3**) and chromenopyrimidine (**4**) derivatives were obtained. Alternatively, **3** could be obtained as sole product, when the reaction was carried out in boiling water. Using the simple reaction of compound (**3**) with ethyl cyanoacetate in ethanolic sodium ethoxide at room temperature,[16] pyrido[2,3-*d*]pyrimidine (**11**) and chromeno[2,3-*d*]pyrimidine (**12**) derivatives were obtained. On the other hand, the Vilsmeier reaction[19] of **1** using a complex of dimethylformamide (DMF)-$POC1_3$ gave the dimethylaminomethylidene derivative (**13**), which on reaction with phenylhydrazine in $CHC1_3$ at room temperature[20] yielded the phenylhydrazone derivative (**14**). The analytical and mass spectral data of

13 were consistent with the molecular formula $C_{14}H_{15}N_3O_3$.

Furthermore, benzylpyrimidinetrione (**1**) was allowed to react with ethyl cyanoacetate in ethanolic sodium ethoxide at elevated temperature.[13] It is important to note that this reaction under the above conditions leads to the formation of hydrolysed product, 3-benzyl-2*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7(1*H*,3*H*, 6*H*)-tetrone (**15**), in this case, it was impossible to isolate the unhydrolysed intermediate. While, the reaction of **1** with phosphorous oxychloride gave the pyrimido[4',5':4,5]furo[2,3-*d*]pyrimidine (**16**). Interestingly, the dimer (**17**) was obtained by action of AcOH/piperidine on compound (**1**) in ethanol. Acylation of **17** in boiling acetic anhydride[13] yielded pyrimidopyranopyrimidinetrione derivative (**18**).

EXPERIMENTAL

Mps are uncorrected. IR spectra (KBr discs) were recorded on a FT-IR 1650 (PERKIN ELMER) spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer in DMSO-d_6 using TMS as an internal standard. The EIMS were obtained with a Varian MAT 311A instrument. Elemental analyses were performed at the microanalytical unit of Cairo University. Compounds (**1**) and (**2**) were prepared by reported procedure.

*1-Benzyl-5-arylmethylidene-2,4,6(1H,3H,5H)-pyrimidinetriones (**2**,**3**). General procedure.*

To a boiling solution of l-benzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**1**) (4.36 g , 0.02 mol) in water (500 mL), benzaldehyde and\or salicylaldehyde (0.02 mol) was added dropwise with stirring and the reaction mixture was refluxed for 0.5 h. The precipitate was collected by filtration and recrystallized from an appropriate solvent to give **2** and **3**, respectively. IR (**3**)**:** 3410 (υOH) phenolic; 3302 (υNH); 1720, 1689 (υC=O) and 1620 cm^{-1} (υC=C). ^{1}H NMR (DMSO-d_6) (**3**) : δ 11.69(1H, s, NH), 10.18(1H, s, OH phenolic), 8.95(1H, s, C=CH), 7.30-6.85(9H, m, Ar-H), 4.97(2H, s, CH_2Ph).

*3-Benzyl-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (**4**).*

To a solution of **1** (2.18 g, 0.01 mol) in ethanol (25 mL) was added an ethanolic solution (10 mL) of salicylaldehyde (1.22 g, 0.01 mol), and the resulting mixture was refluxed for 2 h. The solid separated on hot was filtered and recrystallized from DMF to give **3**, (0.8 g, 25%), mp 320 ^{0}C, while the semi-solid (that separated on dilution of the mother liquour with water and solidified on standing overnight in a cooler) was collected by filtration, dried and recrystallized from ethanol to afford **4**, (1.82 g, 60%), mp 265 ^{0}C. IR (**4**)**:** devoid of the υOH(phenolic) and showed 1712, 1696 (υC=O); 1638 cm^{-1} (υC=C). MS: *m/z* 304 (M^+), 218, 132 (base peak).

*1-Benzyl-5-(1-hydroxypropylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione (**5**).*

To a stirred and cold (0^0C) solution of **1** (2.18 g, 0.01 mol) in dry pyridine (30 mL), propanoyl chloride (0.92 g, 0.01 mol) was added dropwise. The mixture was stirred at rt for 18 h. The reaction mixture was quenched by addition of ice, water, and the semi-solid (that separated on acidification with 5% hydrochloric acid until the stirred solution was just acidic to litmus, and solidified on standing overnight in a

cooler) was collected by filtration, dried, and recrystallized from ethanol to give **5**, (1.86 g, 68%), mp 174 ^{0}C. IR: 3460 (υOH enolic); 3190 (υNH); 1753, 1681 (υC=O) and 1620 cm^{-1} (υC=C). MS: the molecular ion and base peak at *m/z* 274. ^{1}H NMR (DMSO-d$_6$) : δ 12.25(1H, s, NH-br), 7.55-7.16(5H, m, Ar-H), 4.95(2H, s, C<u>H</u>$_2$Ph), 3.10-3.07(2H, q, J=7 Hz, C<u>H</u>$_2$CH$_3$), 1.16-1.08(3H, t, J=7 Hz, CH$_2$C<u>H</u>$_3$).

*N`-[3-Benzyl-2,6-dioxo-5-benzylidenetetrahydro-4(1H)-pyrimidinylidene]formic hydrazide (**6**).*

To a solution of **2** (3.06 g, 0.01 mol) in DMF (20 mL), 85% hydrazine hydrate (0.59 mL, 0.01 mol) was added and the reaction mixture was refluxed for 0.5 h and then concentrated under a reduced pressure. To the residue, water (15 mL) was added, the semi-solid (that separated out and solidified on standing at room temperature) was collected by filtration, dried and recrystallized from DMF to give **6**, (2.78 g, 80%), mp 335 ^{0}C. MS: *m/z* 348 (M$^+$). IR: 3231 (υNH); 1721, 1692, 1625 (υC=O) and 1590 cm^{-1} (υC=N).

*8-Benzyl-4-phenylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione (**7**).*

A solution of **6** (3.48 g, 0.01 mol) in 20 mL of glacial acetic acid was refluxed for 1 h. The excess acetic acid was removed under a reduced pressure. The solid obtained was filtered, dried and recrystallized from acetic acid to give **7**, (2.34 g, 71%), mp 323 ^{0}C. IR: 3232 (υNH) and 1689, l628 cm^{-1} (υC=O).

*7-Amino-2,4-dioxo-5-phenyl-3,4-dihydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**8**), ethyl 3-benzyl-5-(2-hydroxyphenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (**11**), 3-benzyl-5-ethoxy-1,5-dihydro-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (**12**). General procedure.*

To a freshly prepared sodium ethoxide solution [0.39 g, (0.017 mol) of sodium metal in 100 mL of ethanol], 0.017 mol of malononitrile and\or ethyl cyanoacetate was added with stirring. To this mixture 0.017 mol of **2** and\or **3** was added with continuous stirring for 1 h at rt. 5% Hydrochloric acid was added, until the stirred solution was just acidic to litmus, and then as much ethanol as possible was distilled off under a reduced pressure. The solid separated was recrystallized from an appropriate solvent to give **8**, **11** or **12**, respectively. IR (**8**): 2222 (υCN); 1628 (υC=O); 3225 (υNH$_2$) and 3464, 3325 cm^{-1} indicates that **8** exist in equilibrium with its enol which stabilized through very strong hydrogen bonding. ^{1}H NMR (DMSO-d$_6$) (**8**) : δ 8.01(1H, s, NH-br), 7.93-7.57(5H, m, Ar-H), 3.99, 3.94(3H, s, NH$_2$+OH enolic). IR (**11**)**:** 3425 (υOH) phenolic; 3220, 3110 (υNH); 1713, 1688, 1636 cm^{-1} (υC=O). ^{1}H NMR (DMSO-d$_6$) (**11**) **:** δ 11.72, 11.40 (2H, s, 2xNH), 7.31-6.94(9H, m, Ar-H), 5.02(1H, s, OH phenolic), 4.89(2H, s, C<u>H</u>$_2$Ph), 4.14-4.07 (2H, q, J=7 Hz, C<u>H</u>$_2$CH$_3$), 2.25-2.16(3H, t, J=7 Hz, CH$_2$C<u>H</u>$_3$). IR (**12**): 3290 (υNH); 1721, 1687 (υC=O); 1624 cm^{-1} (υC=C). MS (**12**): *m/z* 306 (M-CH$_3$CHO) which, in turn, eliminated benzyl radical to afford the base peak at *m/z* 215. ^{1}H NMR (DMSO-d$_6$) (**12**) : δ 12.44(1H, s, NH), 7.40-6.79(9H, m, Ar-H), 4.95(2H, s, C<u>H</u>$_2$Ph), 4.65(1H, s, CH), 4.15-4.08(2H, q, J=7 Hz C<u>H</u>$_2$CH$_3$), 1.10-1.03(3H, t, J=7 Hz CH$_2$C<u>H</u>$_3$).

*8-Benzyl-2-hydrazino-4-phenyl-2H-pyrimido[4,5-d][1,3]thiazine-5,7(6H,8H)-dione(**9**).*

A solution of **2** (3.06 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in ethanol (50 mL) and few drops of dry pyridine was refluxed on a steam bath for 3 h. The reaction mixture was concentrated to half

Table 1. Physical data of prepared compounds

Compound	mp(^{o}C) (Solvent)	Yield (%)	Formula	Analysis	Found/Calcd		
					C	H	N
3	320 (DMF)	25	$C_{18}H_{14}N_2O_4$	F	67.17	4.45	8.60
				C	67.07	4.38	8.69
4	265 (Ethanol)	60	$C_{18}H_{12}N_2O_3$	F	71.10	3.81	9.32
				C	71.05	3.97	9.21
5	174 (Ethanol)	68	$C_{14}H_{14}N_2O_4$	F	61.23	5.00	10.29
				C	61.31	5.14	10.21
6	335 (DMF)	80	$C_{19}H_{16}N_4O_3$	F	65.63	4.52	16.20
				C	65.51	4.63	16.08
7	323 (Acetic acid)	71	$C_{19}H_{14}N_4O_2$	F	69.00	4.35	16.86
				C	69.08	4.27	16.96
8	270 (Acetic acid)	55	$C_{14}H_8N_4O_3$	F	60.11	2.79	20.09
				C	60.00	2.88	19.99
9	395 (DMF)	48	$C_{19}H_{17}N_5O_2S$	F	60.23	4.60	18.58
				C	60.14	4.52	18.46
10	244 (Ethanol)	75	$C_{18}H_{16}N_2O_3$	F	70.00	5.30	9.19
				C	70.12	5.23	9.09
11	172 (Toluene)	42	$C_{23}H_{19}N_3O_6$	F	63.80	4.35	9.79
				C	63.74	4.42	9.70
12	210 (Ethanol)	30	$C_{20}H_{18}N_2O_4$	F	68.65	5.09	8.15
				C	68.56	5.18	8.00
13	212 (Ethanol)	50	$C_{14}H_{15}N_3O_3$	F	61.45	5.63	15.28
				C	61.53	5.53	15.38
14	226 (Ethanol)	64	$C_{20}H_{21}N_5O_2$	F	66.21	5.76	19.39
				C	66.10	5.82	19.27
15	265 (Ethanol)	45	$C_{14}H_{10}N_2O_5$	F	58.61	3.50	9.70
				C	58.74	3.52	9.79
16	170 (Benzene)	58	$C_{22}H_{16}N_4O_5$	F	63.39	3.95	13.58
				C	63.46	3.87	13.46
17	204 (Benzene)	65	$C_{22}H_{18}N_4O_5$	F	63.10	4.41	13.49
				C	63.15	4.34	13.39
18	284 (Ethyl acetate)	50	$C_{24}H_{18}N_4O_5$	F	65.23	4.05	12.80
				C	65.15	4.10	12.66

its volume and cooled. The separated solid was filtered off, washed with ethanol and recrystallized from DMF to give **9**, (1.82 g, 48%), mp 395 ^{0}C. IR: 3087, 3199, 3402 (υNH and υNH$_2$); 1709, 1655 (υC=O) 1606 cm^{-1} (υC=N). MS: *m/z* 380 (M+1), 379 (M$^+$) and the base peak at *m/z* 378. ^{1}H NMR (DMSO-d$_6$) : δ 11.29(1H, s, NH), 7.96-7.25(10H, m, Ar-H), 7.30(1H, s, H-2), 5.02(2H, s, C$\underline{H_2}$Ph), 2.51(3H, m, NHNH$_2$).

*1,5-Dibenzyl-2,4,6(1H,3H,5H)-pyrimidinetrione(**10**).*

A solution of **2** (3.06 g, 0.01 mol) and 2-aminobenzenethiol (1.25 g, 0.01 mol) in dry dioxane (50 mL) was boiled under reflux for 18 h. The reaction mixture was filtered while hot, concentrated under vacuum and the solid separated was recrystallized from ethanol to give **10**, (2.31 g, 75%), mp 244 ^{0}C. IR: 3333

(υOH) enolic; 3252 (υNH); 1712,1694 (υC=O) and 1592 cm^{-1}(υC=N). MS: *m/z* 308 (M^+), 309 (M+1), a fragment owing to (M-CH_2Ph) and the base peak at *m/z* 91. ^{1}H NMR (DMSO-d_6) : δ 10.45(1H, s, NH), 7.27-6.90(10H, m, Ar-H), 6.13(1H, s, OH enolic), 4.93(2H, s, CH_2), 3.65(1H, t, J= 5 Hz, CH), 3.00-2.98 (2H, d, J= 5 Hz, CH_2).

*1-Benzyl-5-(dimethylamino)methylidene-2,4,6(1H,3H,5H)-pyrimidinetrione(**13**).*

To a stirred and cold (0^0C) solution of **1** (2.18 g, 0.01 mol) in dimethylformamide (25 mL), a cold mixture of dimethylformamide (2.19 g, 0.03 mol), phosphorus oxychloride (3.06 g, 0.02 mol) was added dropwise. After one hour the reaction mixture was quenched by addition of ice, water and finally with sodium hydrogen carbonate solution (20%).[4] The product was isolated and recrystallized from ethanol to give **13**, (1.37 g, 50%), mp 212 ^{0}C. IR: devoid of a υC=O(formyl) band and showed 3213 (υNH), 1726, 1679 (υC=O) and 1627 cm^{-1} (υC=C). whereas its MS spectrum showed the molecular ion and the base peak at *m/z* 273. ^{1}H NMR (DMSO-d_6) : δ 10.67(1H, s, NH), 8.13(1H, s, C=CH-N), 7.35-7.22(5H, m, Ar-H), 4.92(2H, s, C$\underline{H_2}$Ph), 3.43, 3.27(6H, s, 2xCH_3).

*1-Benzyl-5-(dimethylamino)methylidene-2,4,6(1H,3H,5H)-pyrimidinetrione 6-(N-phenylhydrazone)(**14**).*

Phenylhydrazine (1.08 g, 0.01 mol) was dropped into a cold solution (0-10^{o}C) of **13** (2.73 g, 0.01 mol) in chloroform (60 mL).The mixture was let stand at rt for 1 h and then filtered. The resulting yellow crystals were dried and recrystallized from ethanol to give **14**, (2.32 g, 64%), mp 226 ^{0}C. MS: *m/z* 361 (M-2H), 321 (base peak). ^{1}H NMR (DMSO-d_6) : δ 11.20(1H, s, $\underline{H}$NPh), 8.81(1H, s, NH), 8.13-7.74(10H, m, Ar-H), 7.19(1H, s, C=CH-N), 4.94(2H, s, C$\underline{H_2}$Ph), 3.37, 3.32(6H, s, 2xCH_3). IR: 3249, 3135 (υNH); 1689 (υC=O); 1632 cm^{-1}(υC=C).

*3-Benzyl-5-hydroxy-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione (**15**).*

To a freshly prepared sodium ethoxide solution [0.39 g, (0.017 mol) of sodium metal in 100 mL of ethanol], 1.92 g (0.017 mol) of ethyl cyanoacetate was added with stirring. To this mixture 3.71 g (0.017 mol) of **1** was added with continuous stirring for 1 h at 65 ^{o}C. 5% Hydrochloric acid was added, until the stirred solution was just acidic to litmus, and then as much ethanol as possible was distilled off under a reduced pressure. The solid separated after cooling was recrystallized from ethanol to give **15,** (1.29 g, 45%), mp 265 ^{0}C. ^{1}H NMR (DMSO-d_6) : δ 10.44-10.42(1H, s, OH enolic-br), 7.27 (1H, s, NH), 7.20-7.03(5H, m, Ar-H), 6.10(1H, s, C=CH), 4.95(2H, s, C$\underline{H_2}$Ph). IR: 3631, 3515 (υOH) enolic; 3212 (υNH); 1708,1685 (υC=O); υC=N and υC=C overlaped at 1606 cm^{-1}.

*1,6-Dibenzylpyrimido[4`,5`: 4,5]furo[2,3-d]pyrimidine-2,4,7,9(1H,3H,6H,8H)-tetrone (**16**).*

A mixture of 1-benzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**1**) (2.18 g, 0.01 mol) and $POCl_3$ (15 mL) was refluxed for 1 h, cooled, and treated with crushed ice and finally with sodium hydrogen carbonate solution (20%).[4] The precipitated solid was filtered off, washed with water, dried, and recrystallized from benzene to give **16**, (2.41 g, 58%), mp 170 ^{0}C. IR: 1718-1664 cm^{-1} (υC=O). MS: *m/z* 416 (M^+), 325 (M-

CH_2Ph), 234 (M-2xCH_2Ph) and the base peak at *m/z* 91. ^{1}H NMR (DMSO-d_6) : δ 11.45-11.39(2H, s, 2xOH enolic-br), 8.17, 7.90(2H, s, 2xNH), 7.37-7.07(10H, m, Ar-H), 5.02-4.93(4H, s, 2x$C\underline{H_2}Ph$).

*1-Benzyl-5-(3-benzy/-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinyl)-2,4,6(1H,3H,5H)-pyrimidinetrione(**17**).*

1-Benzyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**1**) (2.18 g, 0.01 mol), acetic acid (1 mL) and piperidine (l mL) in ethanol (70 mL) were left at rt with stirring for 12 h, then refluxed for 5 h. The reaction mixture was concentrated to half its volume, cooled and diluted with water. The separated solid was filtered off, dried and recrystallized from benzene to give **17**, (2.72 g, 65%), mp 204 ^{0}C. IR: 3197, 3154 (υNH); 1725-1622 (υC=O); 1597 cm^{-1}(υC=C). MS: *m/z* 418 (M^+), 285 (M-PhCH_2NCO) which, in turn, eliminated benzyl radical to afford a fragment at *m/z* 194 and the base peak at *m/z* 91. ^{1}H NMR (DMSO-d_6) : δ 13.14, 10.40(2H, s, 2xNH), 7.34-7.21(10H, m, Ar-H), 7.26(1H, s, CH-5), 6.91(1H, s, C=CH), 4.93, 4.18(4H, s, 2x$C\underline{H_2}Ph$).

*1,9-Dibenzyl-4-hydroxy-5-methyl-2H-pyrimido[4`,5`:4,5]pyrano[2,3-d]pyrimidine-2,8,10(1H,9H)-trione (**18**).*

A solution of **17** (4.18 g, 0.01 mol) in acetic anhydride (30 mL) was heated under reflux, then it was evaporated under a reduced pressure. To the residue water (25 mL) was added ; the precipitate was collected by filtration and recrystallized from ethyl acetate to give **18**, (2.21 g, 50%), mp 284 ^{0}C. IR: 3622 (υOH enolic-br); 3233 (υNH); 1775, 1708, 1691 (υC=O); 1649 υC=C; 1604 cm^{-1}(υC=N). MS: *m/z* 442 (M^+), 441 (M-H), which, in turn, eliminated 1-(isocyanatomethyl)benzene radical to leave a fragment at *m/z* 308, followed by benzyl radical fragmentation to afford a fragment at *m/z* 217 and the base peak at *m/z* 149. ^{1}H NMR (DMSO-d_6) : δ 7.30-7.05(10H, m, Ar-H), 5.15(1H, s, OH enolic), 5.09, 4.95(4H, s, 2x$C\underline{H_2}Ph$), 2.09(3H, s, CH_3).

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