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Thioxopyrimidinecarbonitriles as precursors for linked and fused pyrimidine derivatives: synthesis of imidazo-, pyrazoloimidazo-, triazoloimidazopyrimidines and pyrimidoimidazotriazepines

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ABSTRACT

*Alkylation of 6-aryl-4-oxo-2-thioxopyrimidine-5-carbonitriles (**1a-c**) afforded the key intermediates **2a-e,** which underwent further alkylation at N-3 nitrogen atom, upon treatment with α-halofunctionalized compounds, namely: ethyl bromoacetate, chloroacetone, chloroacetylacetone, chloroacetonirile, or monobromomalononitrile to perform 2-alkylthio-6-aryl-5-cyano-4-oxo-3-substituted-3,4-dihydropyrimidines **7-9.** Heating **7-9** with hydrazine hydrate produced imidazo[1,2-a]pyrimidine derivatives **10-15.** Treatment of **10a** with each of ethyl cyanoacetate, ethyl acetoacetate, or acetylacetone gave pyrazoloimidazopyrimidine derivatives **18a,b, 19**, respectively. Compound **10a** reacted with carbon disulphide to give oxazoloimidazopyrimidine**20**. Reaction of the imidazopyrimidine derivative **15a** with glacial acetic acid or thiourea afforded triazoloimidazopyrimidines**21,22**. Also, compound **15a**underwent cycloaddition reaction upon treatment with either of phthalic anhydride or acrylonitrile to give 2-phenyl-4,12-dioxopyrimidino[2``,1``:2`,3`]imidazo[1`,5`:2,3][1,2,4]triazolo[1,5-b]isoindole-3-carbonitrile **(23)** or 8-amino-2-phenyl-4-oxo-7H-pyrimido[2`,1`:2,3]imidazo[1,5-b][1,2,4]triazepine-3-carbonitrile **(24)**, respectively. Imidazo pyrimidines **15d,e** underwent cyclocondensation upon heating with each of formic acid, formamide/ formic acid or ammonium thiocyanate to produce the pyrimido[2,1-f]purine derivatives **25a,b, 26,**and **27**,respectively.*

Keywords: ImidazoPyrimidine; pyrazoloimidazopyrimidine; pyrimidoimidazotriazepine.

INTRODUCTION

Pyrimidine and fused heterocyclic pyrimidine derivatives have received significant attention over the past few years owing to their therapeutic and pharmacological properties[1-6].Imidazopyrimidines are used as anti-HIV [7], antifungustic [8], anticoccdial agents [9], and as modulators of key biological targets [10], alsoa novel series of imidazopyrimidines have been discovered that potently inhibit p38 and suppress the production of TNF-alpha in vivo [11]. Many fused triazolopyrimidines and tetrazolopyrimidines are well known for their antibacterial [12] and antifungal activities [13]. Furthermore, some series of thiazolo[3,2-a]pyrimidine derivatives have been prepared and investigated for their anti-inflammatory [14] and anticancer[15] activities.

On the other hand, functionalized 4-oxo-2-thioxopyrimidines are of considerable importance as excellent precursors for the synthesis of fused pyrimidines. They have been extensively utilized to prepare different fused heterocycles including thiazolo-[16], triazolo-[17], tetrazolo-[18], pyrazolo-[19], and imidazopyrimidines [10,16]. In continuation

of the work directed to synthesis of different heterocyclic compounds [20-23], we herein report on the synthesis and utilization of some 2-substituted alkylmercapto-pyrimidines to attach and annelate a variety of heterocycles to the pyrimidine nucleus.

MATERIALS AND METHODS

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp apparatus. Microanalysis was carried out at the Microanalytical units, Faculty of science, Cairo University. IR spectra were recorded as potassium bromide pellets on Perken Elmer FT/ IR system 2000 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured in DMSO-d6, using JEOL-JNM-EX 270 NMR Spectrometer. Chemical shifts are expressed in δ ppm using TMS as the internal standard. MS were recorded on a HP model MS-5988 spectrometer at electron ionizing energy 70ev.

Synthesis of 6-aryl-5-cyano-4-oxo-2-thioxo(alkylthio)-1,2,3,4-tetrahydropyrimidines 1a-c and 2a-e. The starting compounds **1a-c**and**2a-e** have been synthesized according to reported procedures [17,24].

Synthesis of pyrimidinonehydrazidederivative 3.
To a solution of **2e** (3.15 g, 0.01mole) in dioxane (25ml) hydrazine hydrate (2.5g, 0.05 mole) was added and the reaction mixture was heated, under reflux, for 0.5 h then evaporated under reduced pressure. The solid product thus obtained was crystallized from ethanol as white crystals. Yield 61%, m.p. 238-240 °C. IR (KBr); 3282 (NH), 2204 (CN), and 1683cm^{-1} (CO).H^1-NMR; (DMSO-d$_6$) δ1.70 (br,s, 2H, NH$_2$, D$_2$O-exchangeable), 3.81 (s,2H, CH$_2$), 7.14-7.51(m,5H, Ar), 8.0 (s,1H, NH D$_2$O-exchangeable), and 8.21 ppm(s, 1H, NH, D$_2$O-exchangeable).*Anal*.Calcd for $C_{13}H_{11}N_5O_2S$ (301.32): C, 51.82; H, 3.68; N, 23.24; S,10.64.Found: C, 51.46; H, 3.46; N, 23.12; S, 10.30.

Arylmethylidinehydrazino derivatives 4a,b.
A solution of the hydrazide derivative **3** (3.01g, 0.01mole) in ethanol (20 ml) containing few drops of piperidine was treated with *p*-chlorobenzaldehyde or *p*-methoxybenzaldehyde (0.01mole). The reaction mixture was heated under reflux for 3 h, left to cool, then poured into cold water and acidified with HCl. The solid formed was filtered off and recrystallized from the proper solvent.

Compound 4a, was obtained as yellow crystals recrystallized from ethanol. Yield 78%, m.p. 280-281 °C. IR (KBr); 3208 (NH), 2212 (CN), and 1653 cm^{-1} (CO). MS; m/z (%): M$^+$-Ph; 347 (4.0), 238(73), 212(52.2), 184(71.9), 141(14.5), 127(28.8), 104(52.4), 89(100), 77(37.3), and 51(32.1).*Anal*.Calcd for $C_{20}H_{14}ClN_5O_2S$ (423.88): C, 56.67; H, 3.33; N, 16.52; S, 7.56; Cl, 8.36. Found: C, 56.60; H, 3.19; N, 16.34; S, 7.23; Cl, 7.61.

Compound 4b was recrystallized from dimethylformamide as pale yellow crystals. Yield 70%, m.p. 301-303°C.IR (KBr); 3157 (NH), 2208 (CN), and 1658cm^{-1} (CO).H^1-NMR; (DMSO-d$_6$) δ 3.78 (s, 3H, CH$_3$), 3.82 (s,2H, CH$_2$), 6.90-7.81 (m, 10H, Ar+CH), 8.0 (s,1H, NH D$_2$O-exchangeable), and 8.21 ppm(s, 1H, NH, D$_2$O-exchangeable). MS; m/z (%): M$^+$ 419 (32). *Anal*.Calcd for $C_{21}H_{17}N_5O_3S$ (419.46): C, 60.31; H, 4.09; N, 16.70; S, 7.64. Found: C, 60.22; H, 3.98; N, 16.54; S, 7.34.

2-(5-Thioxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethylthio)-4-oxo-6-phenyl-3,4-dihydro-pyrimidine-5-carbonitrile (5): To a solution of **3** (3.01g, 0.01mole) in ethanol (15ml), potassium thiocyanate (0.97g, 0.01mole) was added and the reaction mixture was heated, under reflux, for 3 h allowed to cool and poured into cold water then acidified with HCl. The formed precipitate was filtered off and recrystallized from ethanol giving yellow crystals. Yield 65%,m.p. 259-260 °C. IR (KBr); 3190 (NH), 2199 (CN), and 1686 cm^{-1} (CO).^{1}H-NMR; (DMSO-d$_6$) δ 2.30(s, 1H, NH, D$_2$O-exchangeable),3.12(s, 2H, CH$_2$), 7.15-7.68(m,6H,ArH+NHD$_2$O-exchangeable) and 8.21ppm(s,1H,NH D$_2$O-exchangeable). MS; m/z (%): M$^+$; 342(85.4). *Anal*.Calcd for $C_{14}H_{10}N_6OS_2$ (342.40): C, 49.11; H, 2.94; N, 24.54; S, 18.72. Found: C, 49.31; H, 2.75; N, 24.42; S, 17.86.

2-(5-Thioxo-4,5-dihydro-1H-[1,3,4]oxadiazol-3ylmethyl-thio)-4-oxo-6-phenyl-3,4-dihydro-pyrimidine-5-carbonitrile (6). To a stirred mixture of **3** (3.01g, 0.01mole) and potassium hydroxide (1.38g, 0.01mole) in ethanol (25ml), carbon disulfide (3.8g, 0.05mole) was added dropwisely. The reaction mixture was allowed to stir for 5 h, heated under reflux for another 8 h, then left to cool and poured into cold water. Acidification with HCl gave a pale yellow precipitate which was filtered off and recrystallized from dilute dimethylformamide.Yield 64%, m.p. 280-282°C.IR (KBr); 3127 (NH), 2218 (CN), 1444(CS), and 1676 cm^{-1} (CO).^{1}H-NMR; (DMSO-d$_6$) δ3.96(s, 2H, CH$_2$),

7.42-7.90 (m, 5H, ArH), 10.03(s, 1H, NH D_2O-exchangeable), and 10.65ppm(s, 1H, NH, D_2O exchangeable). *Anal*. Calcd for $C_{14}H_9N_5O_2S_2$ (343.38): C, 48.97; H, 2.64; N, 20.40; S, 18.67. Found: C, 48.67; H, 2.39; N, 20.23; S, 18.21.

6-Aryl-3-carboethoxymethyl-5-cyano-2-methylthio-4-oxo-3,4-dihydropyrimidines7a-c

Ethyl bromoacetate (1.67g, 0.01 mole) was added to a stirred refluxing mixture of **2a-c**(0.01 mole) and potassium carbonate (1.38 g, 0.01 mole) in ethanol (25 ml) for 2h. The reaction mixture was left to cool, poured into cold water and acidified with HCl. The solid product formed was filtered off and recrystallized from the proper solvent. (Tables 1,2).

Synthesis of 8a-e and 9d,e.

Alkylation of **2a-d** with chloroacetone, chloroacetylacetone, or monobromomalononitrile according to the previous method but using acetone as a solvent in place of ethanol. (Tables 1,2).

6-Aryl-5-cyano-3-cyanomethyl-2-methylthio-4-oxo-3,4-dihydropyrimidines 9a-c.

A mixture of **2a-c** (0.01 mole), potassium carbonate (1.38g, 0.01mole) and chloroacetonitrile (0.76g, 0.01mole) in dimethylformamide (20 ml) was stirred over night at room temperature then poured into cold water and acidified with HCl . The solid formed was filtered off and recrystallized from the proper solvent. (Tables 1,2)

Table (1) Characterization data of S-alkyl-N-substituted pyrimidin-4-one derivatives 7-9

Compound	Molecular formula	Yield%	m.p. (°C) (solvent)	Color	Analysis Calcd. / Found%			
					C	H	N	S
7a	$C_{16}H_{15}N_3O_3S$ 329.08	64	152-155 (Ethanol)	Pale yellow	58.39 58.27	4.59 4.46	12.76 12.54	9.74 9.45
7b*	$C_{16}H_{14}ClN_3O_3S$ 363.04	64	153-155 (Ethanol)	yellow	52.82 52.78	3.88 3.79	11.55 11.24	8.83 8.21
7c	$C_{17}H_{17}N_3O_4S$ 359.09	78	223-225 (Ethanol)	Pale yellow	56.81 56.73	4.77 4.59	11.69 11.48	8.92 8.73
8a	$C_{15}H_{13}N_3O_2S$ 299.07	68	165-170 (Ethanol)	White	60.18 60.08	4.38 4.28	14.04 13.97	10.72 9.84
8b*	$C_{15}H_{12}ClN_3O_2S$ 333.03	72	168-170 (Ethanol)	White	53.97 53.88	3.62 3.49	12.59 12.43	9.62 9.35
8c	$C_{16}H_{15}N_3O_3S$ 329.08	72	151-152 (Ethanol)	Pale green	58.34 58.29	4.59 4.61	12.76 12.56	9.74 9.53
8d	$C_{17}H_{15}N_3O_3S$ 341.08	70	173-175 (Ethanol)	Buff	59.81 59.74	4.43 4.39	12.31 12.22	9.40 8.78
8e	$C_{18}H_{16}ClN_3O_3S$ 389.91	78	233-235 (Ethanol)	White	55.39 55.36	4.10 3.72	10.77 10.71	8.20 8.11
9a	$C_{14}H_{10}N_4OS$ 282.06	70	239-241 (Dioxane)	Yellow	59.56 59.53	3.57 3.60	19.85 19.74	11.36 11.20
9b*	$C_{14}H_9ClN_4O_3S$ 316.02	63	210-212 (Ethanol)	Yellow	53.08 53.02	2.86 2.81	17.69 17.55	10.14 9.61
9c	$C_{15}H_{12}N_4O_2S$ 312.07	68	172-175 (Ethanol)	Yellow	57.68 57.54	3.87 3.83	17.94 17.88	10.27 10.18
9d	$C_{15}H_9N_5OS$ 307.33	62	153-156 (dil DMF)	Brown	58.62 58.31	2.95 3.01	22.79 21.95	10.43 9.14
9e*	$C_{15}H_8ClN_5OS$ 341.77	79	274-275 (Dioxane)	Brown	52.71 52.53	2.36 2.21	20.49 20.34	9.38 9.15

** Cl % for: **7b**, Calcd: 9.76, Found: 8.53; **8b**,Calcd: 10.64, Found: 10.21;**8e**, Calcd: 9.10, Found: 8.21; **9b**,Calcd: 11.21, found: 10.66; **9e**, Calcd: 10.37, Found: 9.48.*

1-Amino-7-aryl-2,5-dioxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyrimidine-6-carbonitriles10a-c.

To a solution of **7a-c** (0.01 mole) in dioxane (25ml), hydrazine hydrate (2.5 g, 0.05 mole) was added. The reaction mixture was stirred under reflux for 3 h then evaporated under reduced pressure. The solid formed was recrystallized from the proper solvent. (Tables 3,4).

1-[(4-Chlorobenzylidene)-amino]-2,5-dioxo-7-phenyl-1,2,3,5-tetrahydroimidazo[1,2-a]- pyrimidine-6-carbonitrile (12)

To a solution **10a** (2.67g, 0.01 mole) in ethanol (20ml),containing few drops of piperidine, *p*-chlorobenzaldehyde (1.40g, 0.01mole) was added and the reaction mixture was refluxed for 3 h, then left to cool and poured into cold

water. The yellow product formed was filtered off and recrystallized from DMF/ethanol. Yield 60%, m.p. 290-293°C.

IR (KBr); 2212(CN), 1654(CO), and 1580 cm^{-1} (N=N),MS; m/z (%): 349/351(100/29.9%).*Anal.*Calcd for $C_{20}H_{12}ClN_5O_2$ (389.79): C, 61.63; H, 3.10; N, 17.97; Cl, 9.09. Found: C, 61.60; H, 3.12; N, 17.93; Cl, 8.76.

Table (2) Spectral data of S-alkyl-N-substituted pyrimidin-4-one derivatives 7- 9

Comp.	IR (KBr) cm^{-1}; ^1H– NMR (δ-ppm); m\z (%)
7a	2217(CN), 1740(CO),1681cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ 1.25 (t, 3H, CH_3), 2.10(s, 3H, CH_3), 4.19(s, 2H, CH_2), 4.22(q, 2H, CH_2),7.65-8.00 ppm (m, 5H, ArH);^{13}C-NMR: 12.3,14.1 (CH_3), 41.1,62.0(CH_2), 94.0(C-5), 117.0(CN), 126.2, 127.3,128.5, 134.0,161.0(sp2 C), 163.1,168 (2CO); MS; m/z: M^+; 329 (9.0).
7b	2213(CN), 1739(CO), 1670 cm^{-1}(CO); ^1H–NMR;(DMSO-d_6) δ 1.41 (t, 3H, CH_3), 2.32(s, 3H, CH_3),3.86(s, 2H, CH_2), 4.22(q, 2H, CH_2),7.10(d,2H,Ar), 7.31(d,2H,Ar); MS;m/z:M^+; 363 (23.6).
7c	2215(CN), 1741(CO),1671 cm^{-1}(CO); ^1H–NMR;(DMSO-d_6) δ 1.40 (t, 3H, CH_3), 2.30(s, 3H, CH_3), 3.61(s,3H,CH_3), 3.86(s,2H,CH_2), 4.21(q,2H,CH_2),6.82(d,2H,Ar), 7.42(d,2H,Ar); MS; m/z: M^+; 359 (42.7).
8a	2219(CN), 1725(CO), 1681 cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ 2.60 (s, 3H, CH_3), 2.71(s, 3H, SCH_3), 2.78 (s, 2H, CH_2), 7.58-7.93 ppm (m, 5H, ArH); MS; m/z: M^+; 299(63.0).
8b	2211(CN), 1724(CO), 1670 cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ 3.10 (s,3H,CH_3), 3.96 (s,2H,CH_2), 4.12(s,1H,NH,D_2Oexcangeable), 7.12 (d, 2H,ArH), 7.33 ppm (d,2H,ArH); MS; m/z: M^+; 333 (65.0) /335(20.30).
8c	2214(CN), 1727(CO), 1663 cm^{-1} (CO);^1H–NMR;(DMSO-d_6) δ 3.12 (s,3H,CH_3), 3.67 (s,3H,CH_3), 4.10 (s,2H,CH_2),4.12(s,1H, NH,D_2O exchangeable), 6.88 (d,2H ,ArH), 7.32 ppm (d,2H, ArH) ; MS; m/z: M^+; 328(72.0).
8d	2218(CN), 1732(CO),1652 cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ2.53 (s, 6H, 2CH_3), 2.73(s, 3H, SCH_3), 5.08 (s, 1H, CH), 7.61-7.94 ppm (m, 5H, ArH); MS; m/z: (M^+- $COCH_3$); 299 (28.88).
8e	2218(CN), 1729(CO), 1665 cm^{-1} (CO);^1H–NMR;(DMSO-d_6) δ 1.41 (t, 3H, CH_3), 2.10 (s, 6H, 2CH_3), 3.21 (q, 2H, CH_2), 5.18 (s, 1H, CH), 7.41 ppm (d, 2H, ArH), 7.53(d,2H, ArH); MS; m/z: (: M^+ /M^{+2}- $COCH_3$); 346/348 (13.58/4.10).
9a	2213(CN), 1681 cm^{-1} (CO); ^1H–NMR; (DMSO-d_6) δ2.74(s, 3H, CH_3), 5.21 (s, 2H, CH_2), 7.61-8.03 ppm (m,5H, ArH); MS; m/z : M^+; 282 (94.4).
9b	2221(CN), 1672 cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ 2.35(s, 3H, CH_3), 4.28(s, 2H, CH_2), 7.13 (d, 2H,ArH), 7.34 ppm (d,2H,ArH);^{13}C-NMR: 14.3 (CH_3),25.8(CH_2), 94.0(C-5), 115.0(CN), 127.3,128.5, 134.0,160.2 (sp2 C), 166.1 (CO); MS; m/z : M^+;316(32.0).
9c	2219 (CN), 1661 cm^{-1} (CO). ^1H–NMR;(DMSO-d_6) δ 2.10(s, 3H, CH_3), 3.81(s,3H,CH_3), 4.22(s, 2H, CH_2), 6.93 (d,2H ,ArH), 7.31ppm (d,2H,ArH).^{13}C-NMR: 14.1 (CH_3),26.4(CH_2), 54.3(CH_3), 94.0(C-5), 115.0(CN), 127.3,128.5, 134.0,160.2 (sp2 C), 163.1 (CO); MS; m/z : M^+;312(42.0).
9d	2212 (CN), 1676 cm^{-1} (CO); ^1H–NMR;(DMSO-d_6) δ 1.98(s, 3H, CH_3), 4.40(s, 1H, CH), 7.49-7.81 ppm (m, 5H, ArH). MS; m/z: M^+; 307(22.0).
9e	2216(CN), 1665 cm^{-1} (CO). MS; m/z: M^+ /M^{+2};341(31.0) / 343(9.6).

Synthesis of 3-p-tolylazo derivative 13.

p-Methyl benzenediazonium chloride, prepared from *p*-toludine (1.08g, 0.01 mole), sodium nitrite (1.035g, 0.015 mole) and HCl, was added to an ice-cold mixture of **10a** (2.67g, 0.01mole) and NaOH (0.4g, 0.01 mole) in pyridine (20 ml). The reaction mixture was allowed to stand at room temperature for 1 h then poured into water. The product obtained was filtered off and recrystallized from ethanol. Yield 68%, m.p. 255-257 °C.

IR(KBr); 3235,3168(NH_2), 2214(CN), 1699, 1654(2CO), and 1595cm^{-1} (N=N). *Anal.*Calcd for $C_{20}H_{15}N_7O_2$ (385.38): C, 62.33; H, 3.92; N, 25.44. Found: C, 62.09; H, 3.63; N, 24.98.

1-Amino-7-aryl-2-methyl-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carbonitriles14a-c,its 3-acetyl analogue 14d and 1,2-diaminoimidazopyrimidinones 15a-e.

The title compounds were synthesized starting from **8a-e** or **9a-e** following method described for the synthesis of compounds **10a-c**. (Tables 3,4).

2-Amino-1-benzyl-5-oxo-7-phenyl-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carbonitrile (16)

The title compound was prepared by aminolysis of **9a** with benzylamine following method described for **10** (Tables3,4).

2-Ethyl-3,5-dioxo-7-phenyl-2,3-dihydro-5H-thiazolo-[3,2-a]pyrimidine-6-carbonitrile (17)

To a stirred mixture of **2e**(3.15g, 0.01 mole) and potassium carbonate (1.38g, 0.01 mole) in ethanol (25 ml), ethylchloroformate (1.08 g,0.01 mole) was added. The reaction mixture was heated under reflux for 2 h, left to cool and poured into water then acidified with HCl. The precipitated product was filtered off and recrystallized from dioxane.(Tables 3,4).

Pyrazolo[1`,5`:3,4]imidazo[1,2-a]pyrimidine-7-carbonitrile derivatives 18a,b and 19 (General Procedure)
To a solution of **(10a**) (2.67g, 0.01 mole) in ethanolic sodium ethoxide solution (0.23g sodium and 20 ml ethanol), an equimolecular amount of either ethylcyanoacetate, ethylacetoacetate, or acetylacetonewas added. The reaction mixture was heated under reflux for 10 h, left to cool and poured into cold water. The solid product obtained was filtered off and recrystallized from the proper solvent. (Tables 3,4).

2-Thioxo-6-oxo-8-phenyl-1H,6H-[1,3,4]oxadiazolo-[1`,5`:3,4]imidazo[1,2-a] pyrimidine-7-carbonitrile (20).
A mixture of **10a** (2.67g, 0.01 mole) and potassium hydroxide (0.56g, 0.01mole) in pyridine (15ml) was treated with 5 ml carbon disulphide. The reaction mixture was heated under reflux for 5 h then cooled and poured into water. Acidification with HCl gave compound **20** as orange crystals which was filtered off and recrystallized from ethanol. (Tables 3,4).

2-Methyl-6-oxo-8-phenyl-1H,6H[1,2,4]triazolo[1`,5`:3,4]imidazo[1,2-a]pyrimidine-7-carbo-nitrile (21).
A stirred solution of 1,2-diaminoimidazo[1,2-a]pyrimidine derivative **15a** (2.66g, 0.01 mole) in acetic acid (10 ml)was heated under reflux for 10 h. The reaction mixture was cooled and poured into water, to afford a solid that was filtered off and recrystallized from dilute dioxane. (Tables 3,4).

2-(Mercapto)-6-oxo-8-phenyl-1H,6H-[1,2,4]triazolo-[1`,5`:3,4]imidazo[1,2-a]pyrimidine-7-carbonitrile (22).
A mixture of **15a** (2.66g, 0.01mole) and thiourea (0.01mole) was fused for 1 h then cooled. The product was triturated with aqueous alcohol, filtered off and finally recrystallized from ethanol (Tables 3,4).

***Alternative procedure*:**
Toa mixture of **15a** (2.66g, 0.01 mole) and potassium hydroxide (0.56g, 0.01mole) in ethanol (15ml), carbon disulphide (3.8g, 0.05mole)was added. The reaction mixture was heated under reflux for 4 h, cooled and poured into cold water then acidified with HCl. The solid formed was filtered off and recrystallized from ethanol. The products obtained by both procedures gave the same m.p., mixed m.p. and spectral data.

2-Phenyl-4,12-dioxopyrimido[2``,1``:2`,3`]imidazo[1`,5`:2,3][1,2,4]triazolo[1,5-b]isoindole-3-carbonitrile(23).
A mixture of **15a** (2.66g, 0.01mole) and phthalic anhydride (0.01mole) was fused for 1 h, then cooled and the product was recrystallized from ethanol (Tables 3,4).

8-Amino-2-phenyl-4-oxo-7H-pyrimido[2`,1`:2,3]imidazol[1,5-b][1,2,4]triazepine-3-carboni- trile (24).
A mixture of **15a** (2.66g, 0.01mole) and acrylonitrile (0.54ml, 0.01mole) in pyridine (20 ml) was heated under reflux for 7 h, left to cool and poured into cold water then acidified with HCl. Crystallization of the separated solid product from ethanol gave **24**(Tables 3,4).

Synthesis ofpyrimido[2,1-f]purine derivatives 25a,b.(General Procedure)
A mixture of **15d,e** (0.01mole) and formic acid (10ml) was heated under reflux for 10 h then left to cool. The brown crystalline product thus formed was filtered off and purified by boiling several times with ethanol (Tables 3,4).

Synthesis ofpyrimido[2,1-f] purine derivative 26.
A mixture of compound **15d** (2.91g, 0.01 mole), formamide (10ml), formic acid (5ml) and dimethylformamide (5ml), was heated under reflux for 10 h and then allowed to cool. The solid product formed was filtered off and recrystallized from dilute dimethylformamide as deep brown crystals (Tables 3,4).

Synthesis of pyrimido[2,1-f] purine derivative 27.
To a solution of **15d**(2.91g, 0.01mole) in acetic acid (20 ml) ammonium thiocyanate (3 g, excess) was added.The reaction mixture was heated under reflux for 6 h, left to cool and poured into water. The solid product was filtered off and recrystallized from ethanol (Tables 3,4).

Table (3) Characterization data of fused pyrimidine derivatives 10a-c and 14-27

Compound	Molecular formula	Yield%	m.p. (°C) (solvent)	color	Analysis Calcd. / Found%		
					C	H	N
10a	$C_{13}H_9N_5O_2$ 267.08	64	200-203 (Ethanol)	Orange	58.41 58.38	3.39 3.36	26.21 26.08
10b*	$C_{13}H_8ClN_5O_2$ 301.69	72	199-200 (Ethanol)	Yellow	51.76 51.72	2.67 2.69	23.21 23.11
10c	$C_{14}H_{11}N_5O_3$ 297.27	68	200-202 (Ethanol)	Orange	56.56 56.53	3.73 3.71	23.56 23.54
14a	$C_{14}H_{11}N_5O$ 265.27	74	229-230 (Ethanol)	white	63.39 63.27	4.18 4.09	26.40 26.21
14b*	$C_{14}H_{10}ClN_5O$ 299.72	72	289-290 (dil.DMF)	white	56.10 56.02	3.36 3.29	23.37 23.31
14c	$C_{15}H_{13}N_5O_2$ 295.30	70	233-235 (Dioxane)	white	61.01 59.98	4.44 4.41	23.72 23.69
14d	$C_{16}H_{13}N_5O_2$ 307.11	68	200-203 (ethanol)	Buff	62.53 62.49	4.26 4.23	22.79 22.81
15a	$C_{13}H_{10}N_6O$ 266.26	61	304-306 (dil DMF)	Brown	58.64 58.60	3.79 3.75	31.56 31.54
15b*	$C_{13}H_9ClN_6O$ 300.70	67	165-168 (Dioxane)	Brown	51.92 51.80	3.02 3.06	27.95 27.11
15c	$C_{14}H_{12}N_6O_2$ 296.19	60	172-177 (Dioxane)	Brown	56.75 56.69	4.08 4.05	28.36 28.32
15d	$C_{14}H_9N_7O$ 291.27	68	226-228 (Ethanol)	Brown	57.73 57.66	3.11 3.08	33.66 33.62
15e*	$C_{14}H_8ClN_7O$ 325.71	62	228-230 (Acetic)	Brown	51.63 51.55	2.48 2.45	30.10 3.07
16	$C_{20}H_{15}N_5O$ 341.37	72	214-215 (Dioxane)	Yellow	70.37 70.35	4.43 4.40	20.50 20.48
17**	$C_{16}H_{11}N_3O_4S$ 341.34	78	226-227 (Dioxane)	Yellow	56.30 56.28	3.25 3.22	12.31 12.25
18a	$C_{16}H_8N_6O_2$ 316.27	69	275-276 (Acetic)	Yellow	60.76 60.68	2.55 2.58	26.57 26.48
18b	$C_{17}H_{11}N_5O_3$ 333.30	70	229-230 (Ethanol)	Brown	61.26 61.30	3.33 3.28	21.01 20.97
19	$C_{18}H_{13}N_5O_2$ 331.33	62	200-203 (Ethanol)	Brown	65.25 65.19	3.95 3.90	21.14 21.10
20**	$C_{14}H_7N_5O_2S$ 309.30	62	259-260 (Ethanol)	Orange	54.36 54.33	2.28 2.30	22.64 22.60
21	$C_{15}H_{10}N_6O$ 290.28	66	>300 (Dioxane)	Orange	62.06 61.97	3.47 3.33	28.95 28.56
22**	$C_{14}H_8N_6OS$ 308.32	78	243-245 (Ethanol)	Yellow	54.54 54.23	2.62 2.53	27.26 27.15
23	$C_{21}H_{10}N_6O_2$ 378.34	70	240-242 (Ethanol)	Buff	66.67 66.48	2.66 2.48	22.21 22.15
24	$C_{16}H_{11}N_7O$ 317.29	61	>300 (Ethanol)	Brown	60.56 60.05	3.49 3.60	30.89 29.92
25a	$C_{15}H_9N_7O_2$ 319.28	70	285-286 (Ethanol)	Brown	56.43 56.40	2.84 2.89	30.71 30.63
25b*	$C_{15}H_8ClN_7O_2$ 353.72	73	277-278 (Ethanol)	Brown	50.93 50.89	2.28 2.24	27.72 27.81
26	$C_{15}H_{10}N_8O$ 318.29	73	270-272 (dil. DMF)	Brown	56.60 56.33	3.17 3.10	35.20 35.12
27**	$C_{16}H_{11}N_9OS_2$ 409.45	62	234-235 (Ethanol)	Brown	46.93 46.84	2.71 2.58	30.79 30.66

Cl% for **25b, Calcd; 10.02, Found: 9.40.*

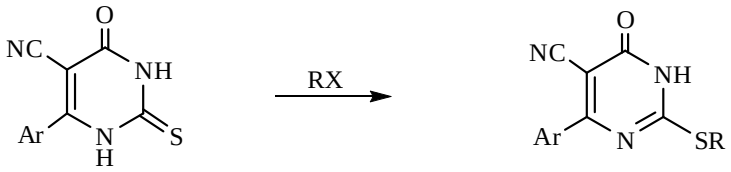
******* S% for: **20**, Calcd: 10.36, Found: 9.72; **22**, Calcd:10.39, Found: 10.13; **27**, Calcd: 15.65, Found: 14.82.*

Table (4) Spectral data of fused pyrimidine derivatives 10a-c and 14-27

Compound	IR (KBr) cm^{-1}; ^1H–NMR (δ-ppm); m\z (%)
10a	3460,3237 (NH_2),2217(CN),1702 (CO),1675 (CO); ^1H-NMR (DMSO-d_6) δ 3.56(s, 2H, NH_2, D_2O-exchangeable), 4.24(s, 2H, CH_2), 7.56-7.64 (m, 5H, ArH);^{13}C-NMR: 47.4(CH_2), 94.2(C-5), 115.0(CN), 127.3,128.5, 136.0,162.4 (sp2 C), 163.1,170.0 (2CO); MS; m/z:M^+; 267(100.0).
10b	3309, 3284(NH_2), 2203(CN),1677(CO),1670(CO); ^1H-NMR;(DMSO-d_6) δ 2.31 (s,2H, NH,D_2O-exchangeable), 3.67 (s,2H,CH_2), 6.85 (d,2H ,ArH), 7.31(d,2H, Ar H) ; MS; m/z: M^+ /M^{+2}; 301 (45.0) /303(13.8).
10c	3293, 3204(NH_2), 2194 (CN), 1686(CO), 1675(CO); ^1H-NMR;(DMSO-d_6) δ 2.11 (s,2H,NH ,D_2O-exchangeable), 3.54(s,3H,CH_3), 3.76 (s,2H,CH_2), 6.85 (d, 2H,ArH) , 7.28(d, 2H, ArH) ; MS; m/z: M^+; 297(37.3).
14a	3333, 3289 (NH_2), 2200 (CN), 1674(CO); ^1H-NMR; (DMSO-d_6) δ 1.99 (s, 3H, CH_3), 3.60(s, 2H, NH_2, D_2O-exchangeable), 4.45 (s, 1H, imidazo H3), 7.49-7.78(m, 5H, ArH); MS; m/z: M^+; 265(52.7).
14b	3409, 3206(NH_2), 2210 (CN), 1679 (CO) ; MS; m/z: M^+; 299(32.6).
14c	3309, 3278(NH_2), 2198 (CN),1676(CO); ^1H-NMR; (DMSO-d_6) δ 1.87 (s, 3H, CH_3), 2.73(s, 2H, NH_2, D_2O-exchangeable), 3.75(s, 3H, CH_3), 7.12-7.78 (m, 5H, 4 ArH+1H, imidazoH3); MS; m/z: M^+; 295(43.0).
14d	3277, 3420 (NH_2), 2206 (CN),1680(CO) ; MS; m/z: M^+; 307(23.40).
15a	3300, 3208 (NH_2), 2198(CN), 1674 (CO); ^1H-NMR; (DMSO - d_6) δ 2.10 (s, 2H, NH_2, D_2O-exchangeable), 3.32(s, 2H, NH_2, D_2O-exchangeable), 6.84-7.78 (m, 6H,5 ArH+1H, imidazo H3);^{13}C-NMR: 73.4(CH), 93.6(C-5), 115.7(CN), 126.1,127.2,128.5, 136.0,139.3,162.0 (sp2 C), 164.2 (CO); MS; m/z :M^+; 266(16.30).
15b	3268, 3104(NH_2), 2208(CN), 1668 (CO); ^1H-NMR;(DMSO-d_6) δ 3.56(s, 2H, NH_2, D_2O-exchangeable), 4.52(s, 1H, imidazoH3), 7.18(s, 2H, NH_2, D_2O-exchangeable), 7.48-8.19(m, 5H, ArH) ; MS; m/z :M^+ - 59; 241(14.26) / 243(4.10).
15c	3302,3280(NH_2),2204(CN),1784 (CO); ^1H-NMR; (DMSO-d_6) δ 2.13(s, 2H,NH_2, D_2O-exchangeable), 3.22(s, 2H, NH_2, D_2O-exchangeable),3.82(s,3H,CH_3), 6.72-7.58 (m, 5H, 4 ArH+1H, imidazo H3); ^{13}C-NMR:54.6(CH_3), 74.2(CH), 93.3(C-5), 115.5 (CN), 126.3,127.2, 128.4, 139.0,159.3,162.0 (sp2 C), 164.0 (CO); MS; m/z :M^+ 296 (24.21).
15d	3475, 3296 (NH_2),2206(CN),1674 (CO); ^1H-NMR; (DMSO-d_6) δ 2.10 (s, 2H, NH_2, D_2O-exchangeable), 3.31(s, 2H, NH_2, D_2O-exchangeable),7.12-7.70 (m, 5H, ArH); MS; m/z:M^{+1}; 292 (82.8).
15e	3451, 3218(NH_2), 2217(CN), 1676 (CO); ^1H-NMR; (DMSO-d_6) δ 2.10 (s, 2H, NH_2, D_2O-exchangeable), 3.21(s, 2H, NH_2, D_2O-exchangeable), 6.85 (d, 2H,ArH) , 7.31(d,2H, Ar H);MS; m/z: M^+ /M^{+2}; 325(12.3) / 327(3.7).
16	3334, 3168(NH_2), 2211 (CN), 1674 (CO); ^1H-NMR; (DMSO-d_6) δ 2.33(s, 2H, NH_2, D_2O-exchangeable), 4.31(s,2H,CH_2),6.51(s, 1H, imidazo H3), 7.13-7.56(m, 10H, ArH);^{13}C-NMR; 39.6(CH_2), 74.2(CH), 93.3(C-5), 115.5 (CN), 126.2,127.4, 128.6,136.0, 139.0, 141.4,151.3,162.0 (sp2 C), 164.0 (CO); MS; m/z: M^+; 341(15.3).
17	2215(CN),1727(CO), 1675(CO);^1H-NMR;(DMSO-d_6)δ1.40(t,3H,CH_3), 4.31(q,2H,CH_2), 4.52(s, 1H,CH),7.10-7.45(m,5H,ArH); MS;m/z: M^+ - COOEt; 269(19.9).
18a	3454, 3240 (NH), 2215, 2213 (CN), 1697, 1669 (2CO); (DMSO-d_6) δ 4.23 (s, 1H, pyrazoloH3), 7.56-7.64 (m, 6H, 5ArH+imidazo H4), 10.67 (s, 1H, NH, D_2O-exchangeable); MS; m/z: M^+; 316 (21.4).
18b	3448, 319 (NH), 2217 (CN), 1699, 1675 (2CO); ^1H-NMR; (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.27 (s, 1H, pyrazolo H3), 7.57-7.67 (m, 6H, 5ArH + imidazo H4), 10.65 (s, 1H, NH, D_2O- exchangeable) ; ^{13}C-NMR: 29.1 (CH3), 55.1 (pyrazolo-C3), 93.3 (Pyrimido-C5), 96.2 (imidazo-C4), 115.5 (CN), 126.2, 127.4, 128.6, 136.0, 162.0 (sp2 C), 163.0, 171.0, 192 (3CO); MS; m/z: M^+ ; 333 (19.1).
19	3464, 3257 (NH), 2215 (CN), 1698, 1666 (2CO); ^1H-NMR; (DMSO-d_6) δ 1.10 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.84 (s, 1H, pyrazolo H3), 7.13-7.42 (m, 6H, 5ArH+imidazo H4); MS; m\z: M^+-$COCH_3$; 289 (9.8).
20	3185 (NH), 2218 (CN), 1676 (CO), 1430 (CS); ^1H-NMR; (DMSO-d_6) δ 2.26 (s, 1H, NH, D_2O- exchangeable), 7.13-7.42 (m, 6H, 5ArH+ imidazo H4); MS; m/z: M^+; 309 (22.0).
21	3316 (NH), 2211 (CN), 1667 (CO); ^1H-NMR; (DMSO-d_6) δ 1.20 (s, 3H, CH_3), 2.31 (s, 1H, NH, D_2O-exchangeable), 7.13-7.36 (m, 6H, 5ArH+imidazo H4); MS; m\z: M^+; 290 (13.5).
22	3248 (NH), 2698 (SH), 2215 (CN), 1676 (CO); ^1H-NMR; (DMSO-d_6) δ 3.59 (s, 1H, imidazo H4), 6.91 (s, 1H, SH, D_2O-exchangeable), 7.49-7.59 (m, 5H, ArH), 8.23 (s, 1H, NH, D_2O-exchangeable);^{13}C-NMR: 93.3 (Pyrimido-C5), 95.2 (imidazo-C4), 115.5 (CN), 126.2, 127.4, 128.6, 133.2,136.0, 162.0, (sp2 C), 163.0 (pyrazolo-C3), 163.8 (CO); MS; m/z: M^+; 308 (22.4).
23	3204 (NH), 2210 (CN), 1732, 1674 (CO) ;^1H-NMR; (DMSO-d_6) δ 7.21-7.95 (m, 10H, 9 ArH+imidazo H6), MS; m/z: 251 (22.0), 212 (19.0), 162 (31.2), 127 (6.8), 104 (62.4), 76 (100).
24	3300, 3270 (NH_2, NH), 2210 (CN), 1676 (CO) ; ^1H-NMR; (DMSO-d_6) δ 2.13 (s, 2H, NH_2, D_2O-exchangeable), 3.30 (s, 1H, NH, D_2O-exchangeable), 4.13 (d, 1H, triazepine H9), 6.91 (s, 1H, imidazo H6), 7.12-7.53 (m, 6H, 5ArH+triazepine H10); MS; m/z : M^+-$C_3H_2N_2$; 251 (42.1).
25a	3431, 3111 (NH_2), 2231 (CN), 1671, 1668 (CO); ^1H-NMR; (DMSO-d_6) δ 3.46 (s, 2H, NH_2, D_2O-exchangeable), 7.58-7.86 (m, 6H, 5ArH+NH, D_2O-exchangeable), 9.36 (s, 1H, pyrimido H2) ; MS; m/z : M^+; 319 (22.3).
25b	3440-3146(NH_2), 2221(CN), 1695 and 1686 (CO);MS; m/z : M^+ /M^{+2}; 353(100) / 355(31.8).
26	3248, 3199, (NH_2), 2210 (CN) and 1671 cm^{-1} (CO),^1H -NMR ;(DMSO-d_6) δ 2.13(s, 2H, NH_2, D_2O-exchangeable), 4.61(s, 2H, NH_2, D_2O-exchangeable), 7.13-7.42 (m, 6H, 5ArH+ purine H-2); MS; m/z :M^+; 318(24.5).
27	3280, 3119(NH, NH_2), 2225 (CN) and 1670 cm^{-1}(CO). ^1H -NMR ;(DMSO-d_6) δ 3.44(s, 2H, NH_2, D_2O-exchangeable), 7.58-7.69 (m, 6H, 5ArH+NH D_2O- exchangeable), 11.07(s, 1H, NH,D_2O-exchangeable), 11.81(s, 2H, NH_2D_2O- exchangeable); 13C-NMR: 93.3(Pyrimido-C5),115.5 (CN), 109,126.2,127.4, 128.6,136.0, 146.0,157.2,162.0, (sp2 C), 164.0 (CO),166.7,169.1(2CS); MS; m/z: M^+ - CH_3N_2S; 334(100).

RESULTS AND DISCUSSION

The synthetic strategy is based on S-alkylation of 6-aryl-4-oxo-2-thioxopyrimidine-5-carbonitriles (**1a-c**) [24] with methyliodide, ethyliodide, or ethyl bromoacetatefollowing reported procedure [17], to afford the key intermediates **2a-e** (Scheme 1).



1a-c

Ar

a = C_6H_5
b = C_6H_4Cl-*p*
c = $C_6H_4OCH_3$-*p*

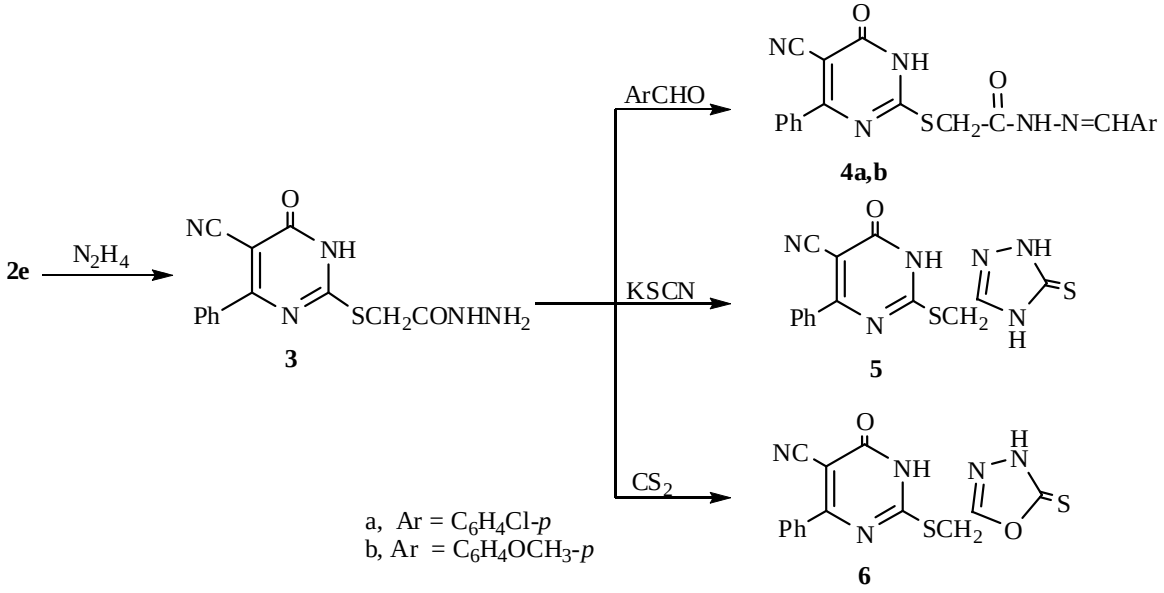
2a-e

Ar		R
a = C_6H_5	,	CH_3
b = C_6H_4Cl-*p*	,	CH_3
c = C_6H_4OMe-*p*	,	CH_3
d = C_6H_5	,	C_2H_5
e = C_6H_5	,	CH_2CO_2Et

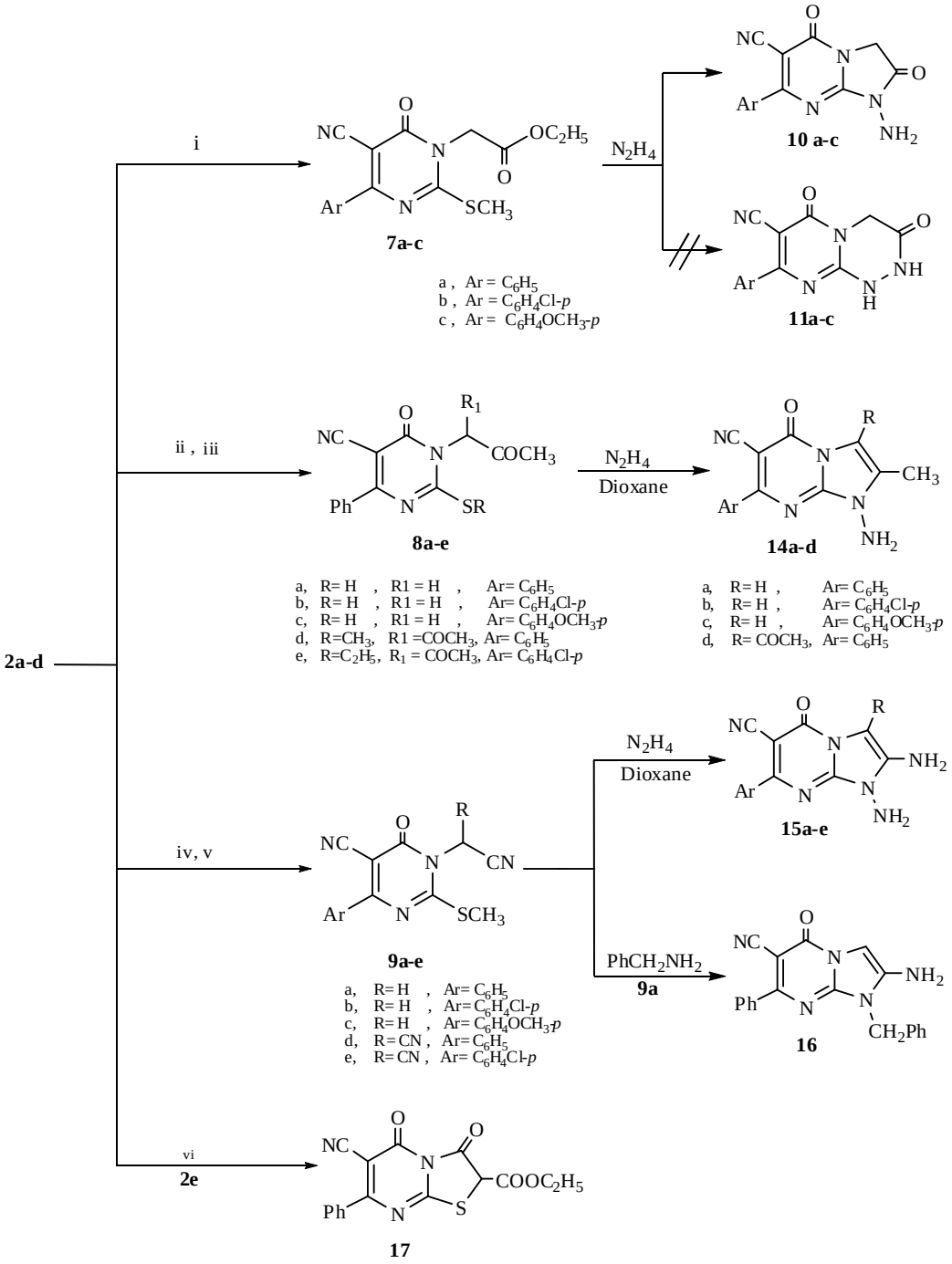
Scheme 1

The synthetic potential of **2e** has been investigated through its conversion into the respective hydrazide**3** upon reaction with hydrazine hydrate in dioxane (Scheme 2). Elemental analysis and spectral data of **3** were compatible with the assigned structure. Condensation of the hydrazide derivative **3** with *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde, in refluxing ethanol, gave the arylmethylidinehydrazino derivatives **4a,b (**Scheme 2). The structure of compounds **4a,b** was confirmed on bases of their spectral and microanalytical data, (Experimental).

Compound **3** was further utilized to connect a triazolethione and oxadiazolethionemoieties to the pyrimidine ring *via* –SCH_2– link, represented by compounds **5** and **6,** respectively. This involved reaction of **3** with potassium thiocyanate in ethanol or condensation with carbon disulphide in ethanolic potassium hydroxide solution (Scheme 2). Compounds **5** and **6**gave expected values in elemental analyses and spectral data, (Experimental). The IR spectrum of **6** displayed absorption bands characteristic of (NH), (CN), (CO), and(CS) at 3057, 3127, 2218, 1665, and 1444cm^{-1}, respectively. The ^{1}H-NMR spectrum (DMSO-d_6) of **6** showed signals at δ 3.96 (s, 2H, CH_2), 7.42-7.90 (m, 5H, ArH), 10.03 (s, 1H, NH D_2O exchangeable) and 10.65 ppm (s, 1H, NH, D_2O exchangeable).



Scheme 2



i : ethyl bromoacetate; ii : chloroacetone; iii : chloroacetylacetone;
iv : chloroacetonitrile; v : monobromomalononitrile; vi : ethylchloroformate.

Scheme 3

Alkylation of 6-aryl-5-cyano-2-methyl (ethyl) thio-4-oxo-4,5-dihydropyrimidines **2a-d**at N-3 nitrogen atom could hopefully provide favorable substrates, to construct fused pyrimidine derivatives, on treatment with α-halofunctionalized compounds, namely: ethyl bromoacetate, chloroacetone, chloroacetylacetone, chloroacetonirile, or monobromomalononitrile. This reaction was conducted in ethanol, acetone, or dimethylformamide, in the presence of potassium carbonate as a base [25], to perform 2-alkylthio-6-aryl-5-cyano-4-oxo-3-substituted-3,4-

dihydropyrimidines **7**,8,and 9 (Scheme 3). Compounds **7-9** gave expected values in elemental analyses and spectral data, (Experimental).

Heating of 6-aryl-3-carboethoxymethyl-5-cyano-2-methylthio-4-oxo-3,4-dihydro-pyrimidines **7a-c**with hydrazine hydrate in dioxane under reflux led to desulphurization and cyclization to produce the sulphur-free compound 1-amino-2,5-dioxo-7-aryl-1,2-dihydro-3H,5H-imidazo[1,2-a]pyrimidine-6-carbonitriles **10a-c** rather than its isomeric pyrimido[2,1-c][1,2,4]triazine structure **11a-c (**Scheme 3**)**.

Assigning the structure **10** for the reaction product was based on its ^{1}H-NMR and MS spectra and by chemical proof as well. ^{1}H-NMR spectrum (DMSO-d_6) for (**10**/**11**) showed, one D_2O exchangeable singlet signal at δ 3.56 assigned to NH_2 group besides the expected CH_2 and phenyl proton signals at δ 4.24 and 7.56-7.64 ppm, respectively, otherwise, two D_2O-exchangeable signals corresponding to two NH groups would be expected. The mass spectrum of the compound in hand showed the molecular ion peak at m/z: 267(100%), a fragment of m/z: 252 (2.9%) corresponding to loss of NH_2 and other fragment ions in agree with structure **10a.**

The chemical proof of structure **10** was obtained from reasonable derivatizations based on its amino and active methylene functions. Thus, **10a** was allowed to condense with *p*-chlorobenzaldehyde to afford the schiff's base **12** (Sheme 4). The IR spectrum of **12** showed disappearance of NH_2 absorption band and appearance of an azomethine band at 1580cm^{-1}. Mass spectrum of compound **12** showed fragments at *m/z:* 349/351(100/29.9%), 238(65.0%), 211(18.3%), and 196(12.2%). Meanwhile, coupling of compound **10a** with *p*-methyl-benzenediazonium chloride gave rise to the 3-*p*-tolylazo derivative **13**, (Scheme4). Compounds **12** and **13** gave expected values in elemental analyses and spectral data, (Experimental).

In analogy to compounds**7**, hydrazinolysis of compounds **8a-e** afforded the imidazo-pyrimidines**14a-d,** (Scheme3), which gave compatible elemental analyses and spectral data,(Experimental).

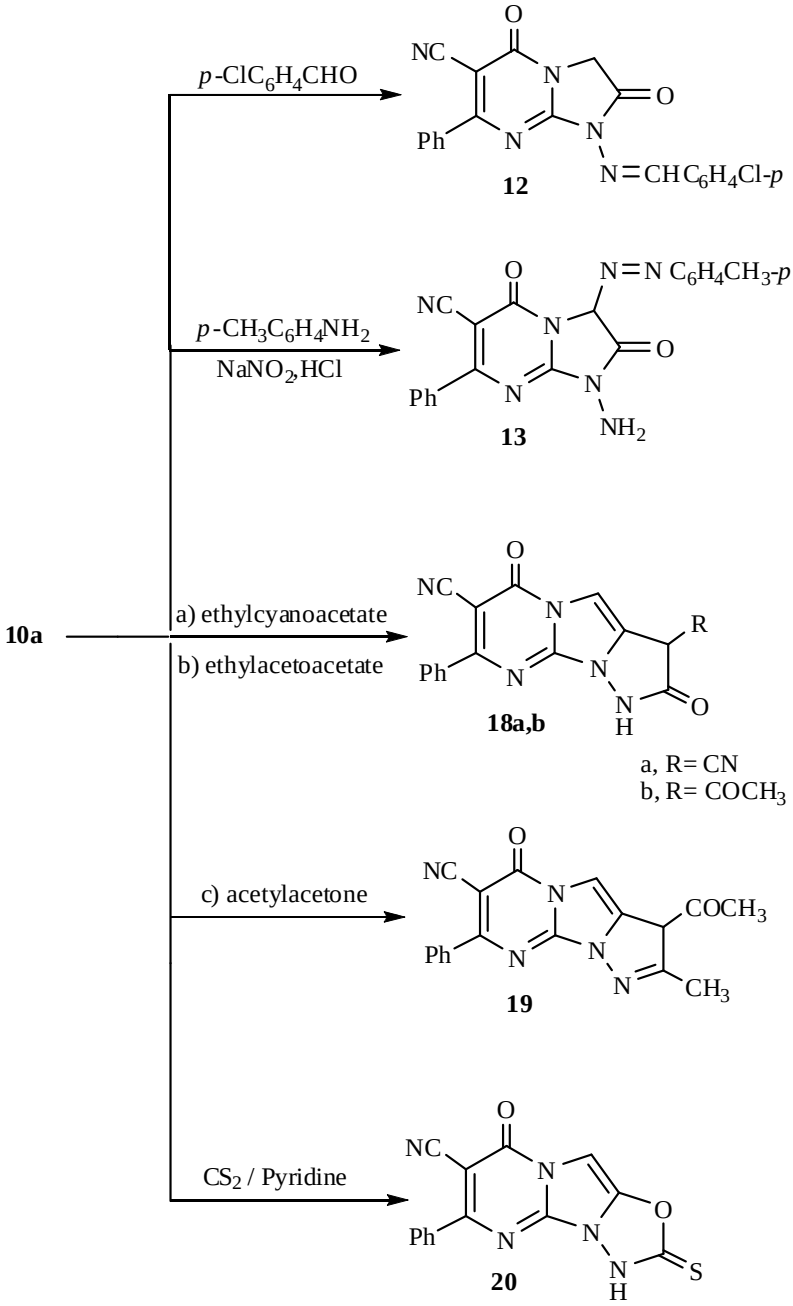
Compounds **9a-e**, having activated nitrile moieties, underwent cyclocondensation upon treatment with hydrazine hydrate under similar reaction conditions to produce the 1,2-diaminoimidazo[1,2-a]pyrimidine-6-carbonitriles **15a-c** and 1,2-diaminoimidazo[1,2-a] pyrimidine-3,6-dicarbonitriles **15d,e** (Scheme3). IR spectra of **15a-e** displayed absorption bands near 3475, 3308, 2206, and 1675 cm^{-1} characteristicof (NH_2), (CN), and (CO), respectively. ^{1}H-NMR (DMSO-d_6) of **15a**, as an example, showed signals at δ 3.56 (s, 2H, NH_2, D_2O exchangeable), 4.52(s, 1H, imidazoH3), 7.18(s, 2H, NH_2, D_2O exchangeable), 7.48-8.19 ppm (m, 5H, ArH). Also, the mass spectrum of **15d**, as another example, showed the $[M+1]^+$ peak at *m/z*: 292(82.8 %).

On the other hand compound **9a** reacted with benzylamine producing 2-amino-1-benzyl-5-oxo-7-phenyl-1,5-dihydro-imidazo[1,2-a]pyrimidine-6-carbonitrile (**16**) (Scheme 3). The spectral data together with the elemental analyses were in agreement with the assigned structure **16,**(Experimental).

Alternatively, synthesis of compound **17** was achieved by reacting of 2-carboethoxy methyl thiopyrimidinone**2e** with ethylchloroformate in ethanolic sodium ethoxide solution (Scheme 3). The IR spectrum of compound **17** revealed no absorption band due to NH and displayed two carbonyl absorption bands on 1675(CO) and 1727 cm^{-1} (ester carbonyl). Also, the mass spectrum of **17** showed a peak at m/z: 269(19.9%) revealing that its molecular ion (not detected) suffered loss of ethyl carboxylate radical $^{\cdot}COOC_2H_5$,(Experimental).

Treatment of 1-aminoimidazopyrimidinone **10a** with an equimolar amount of each of ethyl cyanoacetate, ethyl acetoacetate, or acetylacetone in ethanolic sodium ethoxide solution produced 2,6-dioxo-8-phenyl-1,2,3,6-tetrahydropyrazolo[1`,5`:3,4]imidazo[1,2-a] pyrimidine-3,7-dicarbonitrile (**18a**), 3-acetyl-2,6-dioxo-8-phenyl-1,2,3,6-tetrahydropyrazolo[1`,5`:3,4]-imidazo[1,2-a]pyrimidine-7-carbonitrile (**18b**), or 3-acetyl-2-methyl-6-oxo-8-phenyl-1H,6H-pyrazolo [1`,5`:3,4]imidazo[1,2-a]pyrimidine-7-carbonitrile (**19**) respectively (Scheme 4).

Elemental analyses and spectral data of compounds **18a,b**and **19** were in full agreement with the proposed structures, (Experimental). Appearance of bands at 2215, 2213 cm^{-1} (two CN), 1697 and 1669 cm^{-1} (two CO) in the IR spectrum of compound **18a** supported its formation. Also, its ^{1}H-NMR (DMSO-d_6) showed signals at δ 4.23(s, 1H, imidazo H4), 7.56-7.64(m, 6H, 5ArH + pyrazoloH3), and 10.67 ppm (s, 1H, NH, D_2O exchangeable). The mass spectrum of **19** showed a peak at *m/z*: 289(9.8%) corresponding to loss of acetyl radical $^{\cdot}COCH_3$ and other fragments supporting its formation.



Scheme 4

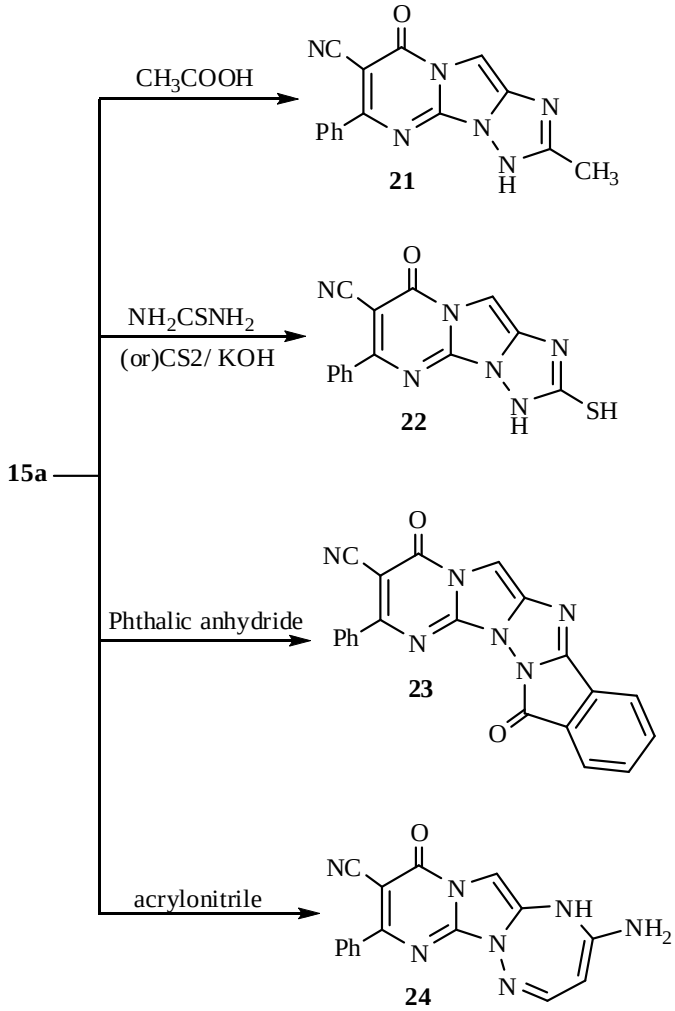
Compound **10a** reacted with carbon disulphide in pyridine to afford 6-oxo-8-phenyl-2-thioxo-1H,6H-[1,3,4]oxadiazolo-[1`,5`:3,4]imidazo[1,2-a]pyrimidine-7-carbonitrile (**20**) (Scheme 4). Elemental analyses and spectral data of compound **20** were in agreement with the proposed structure,(Experimental).

The presence of 1,2-diamino moiety in **15a** could be utilized to annulate substituted triazole rings to this imidazopyrimidine ring system. Thus, **15a** underwent cyclization with glacial acetic acid to produce 2-methyl-6-oxo-8-phenyl-1H,6H[1,2,4]triazolo[1`,5`:3,4]-imidazo[1,2-a]pyrimidine-7-carbonitriles (**21**).

Also, fusion of **15a** with thiourea resulted in the formation of the 2-mercapto- triazoloimidazopyrimidine derivative **22**. Meanwhile, cyclization of **15a** into compound **22** has also been achieved by heating with carbon disulphide in

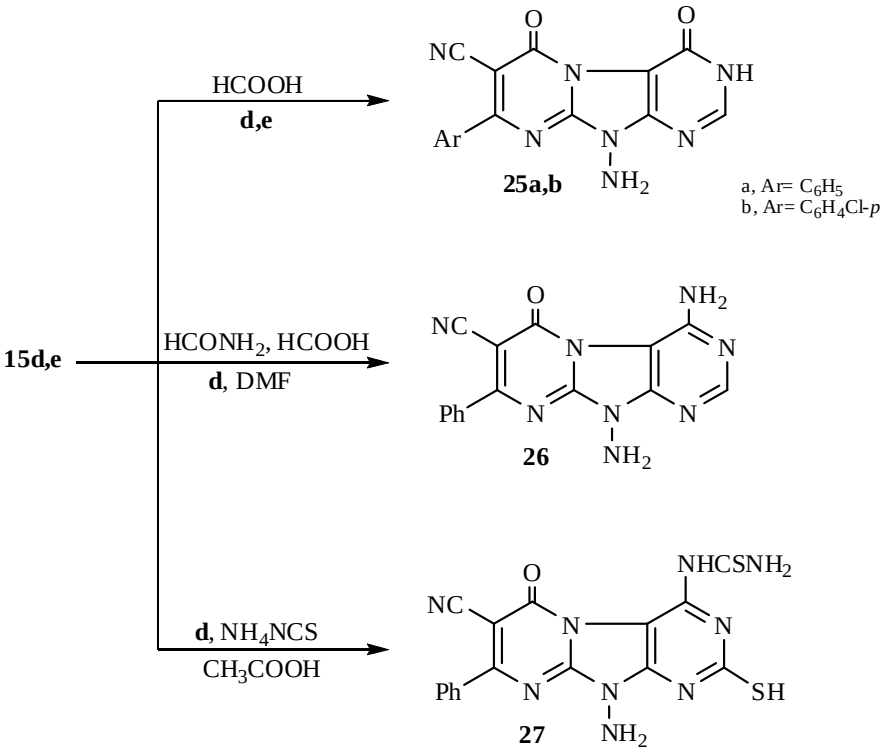
ethanolic potassium hydroxide solution (Scheme 5). The structure of compounds **21** and **22** were supported by the disappearance of the characteristic NH_2 absorption bands in the IR spectra, and by compatible ^{1}H-NMR and MS spectra, (Experimental).

The imidazopyrimidinone derivative **15a** underwent cycloaddition reaction, upon treatment with each of phthalic anhydride or acrylonitrile to give 2-phenyl-4,12-dioxopyrimidino[2``,1``:2`,3`]imidazo[1`,5`:2,3][1,2,4]triazolo[1,5-b]isoindole-3-carbonitrile (**23**) or 8-amino-2-phenyl-4-oxo-7H-pyrimido[2`,1`:2,3]imidazo[1,5-b][1,2,4]triazepine-3-carbonitrile (**24**), respectively (Scheme 5). Elemental analyses and spectral data of compounds **23** and **24** were compatible with assigned structures, (Experimental).



Scheme 5

Imidazopyrimidinones**15d,e**, having an enaminonitrile moiety, underwent cyclocondensation reactions upon heating under reflux with each of formic acid, formamide/formic acid in dimethylformamide or with ammonium thiocyanate in acetic acid to produce the pyrimido[2,1-f] purine derivatives **25a,b, 26**,and **27,** respectively, **(**Scheme 6**).**



Scheme 6

The IR spectra of **25a,b**, **26** and **27** displayed absorption bands around 3150-3440, 2231-2210, and 1695-1664 cm^{-1} characteristicof (NH_2), (CN), and (CO), respectively. The ^{1}H-NMR spectrum (DMSO-d_6) of **25a**, as a representative example, showed signals at δ 3.46(s, 2H, NH_2, D_2O-exchangeable), 7.58-7.86 (m, 6H, 5ArH+NH, D_2O-exchangeable), and 9.36 ppm(s,1H, pyrimido H2). The spectral data together with the elemental analyses were in agreement with the assigned structures **25-27**,(Experimental).

CONCLUSION

A simple and efficient synthesis of new substituted imidazo-, Pyrazoloimidazo-, Triazoloimidazopyrimidines and Pyrimidoimidazotriazepines have been synthesized owing to their expected therapeutic and pharmacological properties. The structures of the newly synthesized compounds were proven by both spectral and chemical methods.

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