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Synthesis of pyrimidine and azolopyrimidines as biodynamic agents†

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5-Cyano-6-(4-pyridyl)-2-thiouracil **1** has been synthesized and used as a precursor for the synthesis of mono and bicyclic pyrimidine derivatives **2-10** to evaluate their biodynamic properties.

Pyrimidines, being an integral part of DNA and RNA imparts to diverse pharmacological properties, as effective bactericide, fungicide, viricide, insecticide and meticide[1-3]. Certain pyrimidine derivatives are also known to display antimalarial[4], antifilarial[5] and antileishmanial[6] activities. The biodynamic property of this ring system prompted us to design pyrimidine derivatives simulating pharmacophore and substituents responsible for diverse pharmacological activities.

5-Cyano-6-(4-pyridyl)-2-thiouracil **1** was used as a precursor to synthesize various pyrimidine derivatives from the condensation-cyclization reaction of 4-pyridyl carboxaldehyde, ethyl cyanoacetate and thiourea in the presence of potassium carbonate using ethanol as solvent. Alkylation of **1** with an equimolar amount of alkyl halide at 0-5°C in DMF using potassium carbonate as a base, produced 2-alkylthio-4-oxo-6- (4-pyridyl)-3,4-dihydropyrimidine-5-carbonitriles **2a-f** while reaction with two equivalents of alkyl halide at ambient temperature exclusively yielded 3-alkyl-2-alkylthio-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitriles **3a,b**. Interaction of **1** with 1,2-dibromoethane in DMF in the presence of potassium carbonate led to the formation of 6-cyano-7-(4-pyridyl)-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5(*H*)-one **4**.

Halogenation of 2-methylthio-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile **2a** with phosphoryl chloride provided 4-chloro-2-methylthio-6-(4-pyridyl)pyrimidine-5-carbonitrile **5** which was highly prone to nucleophiles. Reaction of **5** with ethyl 2-mercaptoacetate in the presence of base in alcohol afforded 3-amino-2-carboethoxy-6-carboethoxymethylthio-4-(4-pyridyl)thieno[2,3-*d*]pyrimidine **6** through substitutioncyclization reactions, while reaction with amine under similar reaction conditions yielded only substitution product **7**. The high susceptibility of position-2 in **2a** towards nucleophile, a reaction with excess of hydrazine hydrate at reflux temperature produced 2-hydrazino-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile **8** which underwent condensation-cyclization reactions in formic and acetic acid separately yielding **9a,b** (**Scheme I**).

The hydrazine **8** also on reaction with ethyl ethoxymethylenecyanoacetate and 2-carboethoxy-3,3-dimethylthioacrylonitrile separately yielded 2-(3-amino-4-carboethoxypyrazol-1-yl)-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile **10a** and 2-(3-amino-4-carboethoxy-5-methylthiopyrazol-1-yl)-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile **10b**. Most of the synthesized compounds **1, 2, 3, 4, 5, 8, 9** and **10** were screened[7] for antifungal activity against five human pathogenic fungi namely, *A. fumigatus*, *C. albicans*, *C. neoformans*, *S. schenckii* and *T. mentagrophytes* but only two compounds **1** and **4** were found active at 50 μg/mL concentration against *A. fumigatus*.

These compounds were further evaluated for *in vitro* antileishmanial activity against *L. donovani* promastigote at 25 μg/ml concentration, following the procedure described below. Some of the screened compounds demonstrated significant activity in *in vitro* test.

Promastigotes in the stationary phase of growth (1×10^5 parasite/mL) were inoculated into culture tubes containing Brain Heart Infusion Agar (BHI-Agar) as solid part and Hanks Balance Salt Solution (HBSS) as liquid part. The test chemicals and pentamidine (25 μg/mL, DMSO/PBS) were added to the above tubes respectively. The inhibitory effect of test compounds was compared with standard drug

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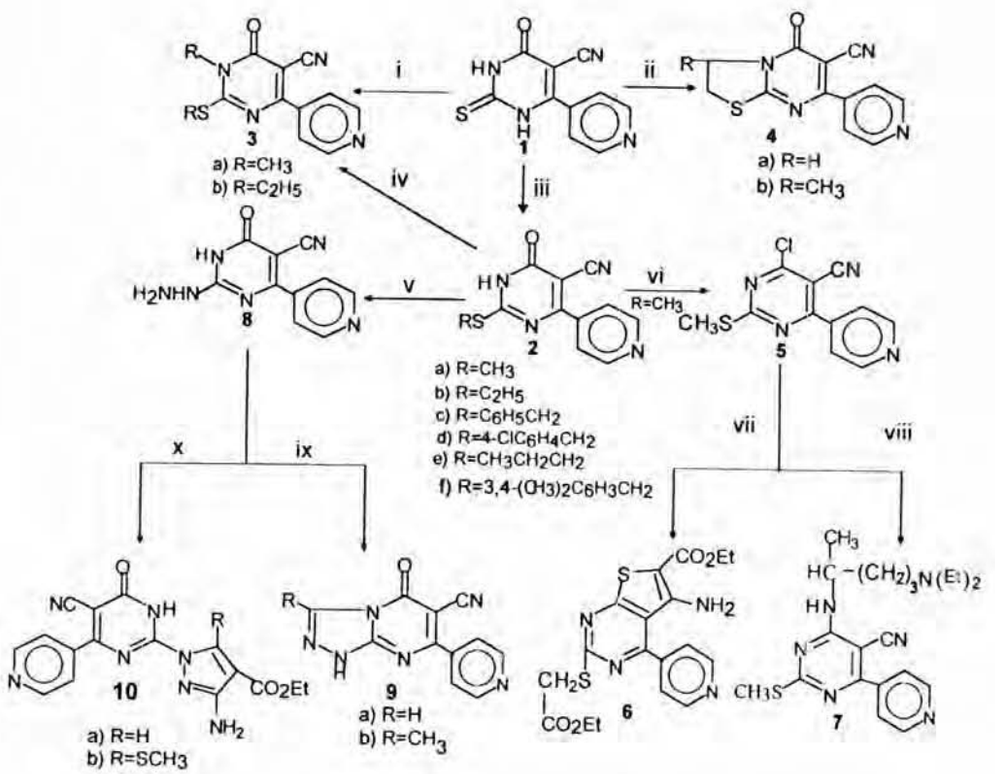

Reagents : i) 2RX / K_2CO_3 ii) R-CH(Br)-CH_2Br, iii) RX , iv) RX / K_2CO_3, v) N_2H_4, vi) $POCl_3$, vii)$SHCH_2CO_2Et$, viii) H_2N-CH(CH_3)-$(CH_2)_3N(Et)_2$,ix) RCO_2H x)EtOCH=C(CN)CO2Et or $(H_3CS)_2C$=C(CN)CO_2Et

Scheme I

Table I — *In vitro* Antileishmanial activity of the compounds tested at 25 μg/mL concentration against *L. donovani*

Compd	Inhibition (%)	Compd	Inhibition (%)
1	62	**4a**	68
2a	62	**4b**	75
2b	19	**5**	88
2c	NI	**8**	37
2d	75	**9a**	50
2e	62	**9b**	68
2f	62	**10a**	68
3a	75	**10b**	62
3b	50	Pentamidine (standard drug)	100

NI=No inhibition

pentamidine. The whole operation was carried out asceptically in a UV Chamber and tubes were inoculated for 5 days at 22°C. The antileishmanial activity of each compound was determined in triplicate by counting the number of live parasites per field microscopically and inhibition percentage was calculated and compared with standard drug Pentamidine by using Z statistic.

The activity profile of all the screened compounds is presented in **Table I**. As it is evident from the activity profile that compound **5** is the most potent amongst all and inhibited the growth of parasite to 88%, while **2d, 3a** and **4b** displayed inhibition to 75%. Except compounds **2b** and **8** all other compounds demonstrated moderate inhibition (50-68%) at the same concentration.

Experimental Section

Melting points were determined on an electro-thermal apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Perkin-Elmer AC-1 spectrometer (ν_{max} in cm^{-1}), ^1H NMR spectra on Perkin-Elmer (400 MHz) or a Bruker WM (300 MHz) NMR spectrometer using TMS as a reference

Table II — Characterization data of compounds **2b-f**

Compd	m.p. °C	Yield (%)	Mol. formula*	Spectral data
2b	268-72	29	$C_{12}H_{10}N_4OS$	MS: m/z 286 (M^+); IR: 1689 (>C=O), 2223 (C≡N), 3425 (NH); ^{1}H NMR(DMSO-d_6): 12.12 (bs, 1H, NH), 8.81 (d, 2H, Ar–H), 7.83 (d, 2H, Ar–H), 3.23 (q, 2H, CH_2), 1.34 (t, 3H, CH_3)
2c	283-86	62	$C_{17}H_{12}N_4OS$	MS: m/z 320 (M^+); IR: 1695 (>C=O), 2231 (C≡N), 3419 (NH); ^{1}H NMR(DMSO-d_6): 12.09 (bs, 1H, NH), 8.81 (d, 2H, Ar–H), 7.90 (d, 2H, Ar–H), 7.48-7.27 (m, 5H, Ar–H), 4.60 (s, 2H, CH_2)
2d	318-22	55	$C_{17}H_{11}ClN_4OS$	MS: m/z 356 (M^+); IR: 1691 (>C=O), 2218 (C≡N), 3430 (NH); ^{1}H NMR(DMSO-d_6): 12.11 (bs, 1H, NH), 8.78 (d, 2H, Ar–H), 7.89 (d, 2H, Ar–H), 7.37 (d, 2H, Ar–H), 7.22 (d, 2H, Ar–H), 4.38 (s, 2H, CH_2)
2e	265-70	27	$C_{13}H_{12}N_4OS$	MS: m/z 272 (M^+); IR: 1691 (>C=O), 2223 (C≡N), 3440 (NH); ^{1}H NMR(DMSO-d_6): 12.13 (bs, 1H, NH), 8.74 (d, 2H, Ar–H), 7.76 (d, 2H, Ar–H), 3.10 (t, 2H, CH_2), 1.64 (m, 2H, CH_2), 0.88 (t, 3H, CH_3)
2f	278-80	63	$C_{19}H_{16}N_4OS$	MS: m/z 348 (M^+); IR: 1660 (>C=O), 2204 (C≡N), 3432 (NH); ^{1}H NMR(DMSO-d_6): 12.08 (bs, 1H, NH), 8.57 (d, 2H, Ar–H), 7.72 (d, 2H, Ar–H), 7.00-7.10 (m, 3H, Ar–H), 4.25 (d, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.12 (s, 3H, CH_3)

*All the compounds gave satisfactory analyses for C, H and N (±0.5%)

compound (chemical shifts in δ, ppm) and mass spectra on a Jeol-JMS-D300 spectrometer. TLC was performed on glass plates coated with silica gel of different sizes.

5-Cyano-6-(4-pyridyl)-2-thiouracil 1. A mixture of ethyl cyanoacetate (6.78 g, 0.06 moles), thiourea (4.56 g, 0.06 moles), 4-pyridine carboxaldehyde (6.35 g, 0.06 moles), and K_2CO_3 (8.28 g, 0.06 moles) in 100 mL absolute alcohol was refluxed in an oil-bath for 7 hr, cooled and filtered. The precipitate thus obtained was dissolved in hot water, filtered while hot and neutralized with glacial acetic acid. The precipitate obtained was. filtered, washed with water and crystallized from DMF, yield 6.02 g (48%), mp 199-204°C; MS: m/z 230 (M^+); IR: 1693 (>C=O), 2237 (C≡N), 3200 (NH); ^{1}HNMR (DMSO-d_6): 13.22 (s, H, –NH), 8.80 (d, 2H, Ar–H), 7.65 (d, 2H, Ar–H) (Found: C, 52.04; H, 2.83; N, 24.19. $C_{10}H_6N_4OS$ requires C, 52.2; H, 2.60; N, 24.4%).

2-Methylthio-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 2a. To a mixture of **1** (0.5 g, 2.17 mmoles) and K_2CO_3 (0.4 g, 2.80 mmoles) in DMF (6 mL) maintained at 0°C, methyl iodide (0.32 g, 2.25 mmoles) was added dropwise with stirring. The mixture was stirred for 4 hr and poured on cold water with vigorous stirring. The aqueous solution after filtration was neutralized with acetic acid. The precipitate obtained was crystallized from DMF, yield 0.42 g (39%) mp 250°C; MS: (m/z) 244 (M^+); IR: 1670 (>C=O), 2210 (C≡N), 3405 (NH); ^{1}H NMR (DMSO-d_6): 12.12 (bs, 1H, NH), 8.80 (d, 2H, Ar–H), 7.85 (d, 2H, Ar–H), 2.64 (s, 3H, $-CH_3$) (Found: C, 54.03; H, 3.21; N, 22.45. $C_{11}H_8N_4OS$ requires C, 54.06; H, 3.28; N, 22.9%).

Compounds **2b-f** were prepared similarly and their characterization data are presented in **Table II**.

3-Methyl-2-methylthio-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 3a. A mixture of **1** (0 5 g, 2.17 mmoles), methyl iodide (0.65 g, 4.48 mmoles), and K_2CO_3 (0.6 g, 4.35 mmoles) was stirred in DMF (6 mL) for 4 hr at room temperature. The mixture was diluted with water and the precipitate obtained was filtered and dried. The crude product was crystallized from $CHCl_3$, yield 0.18 g (15%), mp >250°C; MS: m/z 258 (M^+); IR: 1690 (>C=O), 2220 (C≡N); ^{1}H NMR (DMSO-d_6): 8.80 (d, 2H, Ar–H), 7.85 (d, 2H, Ar–H), 3.64 (s, 3H, $-CH_3$), 2.60 (s, 3H, $-CH_3$) (Found: C, 55.79; H, 3.67; N, 21.23. $C_{12}H_{10}N_4OS$ requires C, 55.80; H, 3.88; N, 21.70%).

3-Ethyl-2-ethylthio-4-oxo-6- (4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 3b. It was prepared from the reaction of **1** (0.5 g, 2.17 mmoles), ethyl iodide (0.7 g, 4.48 mmoles), and K_2CO_3 (0.6 g, 4.35 mmoles) in DMF (6 mL) as described in the preceding experiment. The crude product was crystallized from $CHCl_3$, yield 0.49 g (79%), mp >250°C; MS: m/z 286 (M^+); IR: 1690 (>C=O), 2220 (C≡N); ^{1}HNMR ($CDCl_3$): 8.83 (d, 2H, Ar–H), 7.94 (d, 2H, Ar–H), 3.84 (q, 2H, $-CH_2$), 3.63 (s,

3H, $-CH_3$), 3.22 (q, 2H, $-CH_2$), 2.72 (d, 3H, $-CH_3$) (Found: C, 58.85; H, 4.87; N, 20.23. $C_{14}H_{14}N_4OS$ requires C, 58.70; H, 4.89; N, 19.60%).

6-Cyano-7-(4-pyridyl)-2,3-dihydrothiazolo[3,2-*a*] pyrimidin-5(*H*)-one 4a. A ternary mixture of **1** (0.5 g, 2.17 mmoles), 1,2-dibromomethane (0.41 g, 2.18 mmoles), and K_2CO_3 (0.6 g, 4.35 mmoles) in DMF (6 mL) was heated on the steam-bath for 3 hr, cooled and poured on cold water with vigorous stirring. The precipitate thus obtained was filtered, dried and crystallized from aqueous methanol, yield 0.14 g (16%), mp 229-232°C; MS: m/z 256 (M^+); IR: 1662 (>C=O), 2221 (C≡N); ^{1}HNMR ($CDCl_3$): 8.81 (d, 2H, Ar–H), 7.86 (d, 2H, Ar–H), 4.63 (t, 2H, $-CH_2$), 3.62 (t, 2H, $-CH_2$) (Found: C, 56.40; H, 3.05; N, 21.64. $C_{12}H_8N_4OS$ requires C, 56.25; H, 3.13; N, 21.90%).

6-Cyano-3-methyl-7-(4-pyridyl)-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5(*H*)-one 4b. It was prepared from the reaction of **1** (0.5 g, 2.17 mmoles) and 1,2-dibromopropane (0.44 g, 2.18 mmoles) and K_2CO_3 (0.6g,4.35mmoles) in DMF (6 mL) as described in the preceding experiment. The isolated crude product was crystallized from $CHCl_3$, yield 0.39 g (60%), mp 214-16°C; MS: m/z 270 (M^+); IR: 1670 (>C=O), 2219 (C≡N); ^{1}HNMR ($CDCl_3$): 8.83 (d, 2H, Ar–H), 7.96 (d, 2H, Ar–H), 5.32 (quintet, 1H, –CH), 3.85-3.92 (dd, 1H of $-CH_2$), 3.15 (dd, 1H of $-CH_2$), 1.65 (d, 3H, $-CH_3$) (Found: C, 57.63; H, 3.63; N, 20.76. $C_{13}H_{10}N_4OS$ requires C, 57.80; H, 3.70; N, 20.74%).

4-Chloro-2-methylthio-6-(4-pyridyl)pyrimidine-5-carbonitrile 5. A suspension of **2a** (0.5 g, 2.04 mmoles), in $POCl_3$ (5 mL) was refluxed for 3 hr in an oil-bath and excess solvent was removed *in vacuo*. The viscous liquid was poured on crushed-ice with vigorous stirring and the solution was neutralized with aqueous ammonia. The precipitate thus obtained was filtered, dried and crystallized from $CHCl_3$, yield 0.13 g (32%), mp 160-62°C; MS: m/z 263 (M^+); IR 2223 (C≡N); ^{1}HNMR ($CDCl_3$): 8.86 (d, 2H, Ar–H), 7.89 (d, 2H, Ar–H), 2.67 (s, 3H, $-CH_3$) (Found: C, 50.14; H, 2.31; N, 20.95. $C_{11}H_7N_4SCl$ requires C, 50.19; H, 2.66; N, 21.29%).

3-Amino-2-carboethoxy-6-carboethoxymethylthio-4-(4-pyridyl)thieno[2,3-*d*]pyrimidine 6. A mixture of **5** (0.2 g, 0.75 mmoles), ethyl 2-mercaptoacetate (0.21 g, 1.7 mmoles), K_2CO_3 (0.5 g, 3.6 mmoles) in 20 mL abs. alcohol was refluxed in an oil-bath for 4 hr. The mixture was allowed to cool to room temperature and then worked-up as usual. The precipitate thus obtained was filtered, dried and crystallized from $CHCl_3$, yield 0.17 g (23%), mp 171-73°C; MS: m/z 418 (M^+); IR: 1680, 1734 (>C=O), 3269, 3436 (NH_2); ^{1}H NMR($CDCl_3$): 7.56 (s, 2H, Ar–H), 7.26 (s, 2H, Ar–H), 5.74 (s, 2H, $-NH_2$), 4.23 (q, 2H, $-CH_2$), 4.14 (q, 2H, $-CH_2$), 4.07 (s, 2H, $-CH_2$), 1.37 (t, 3H, $-CH_3$), 1.26 (t, 3H, $-CH_3$) (Found: C, 51.62; H, 4.40; N, 13.21. $C_{18}H_{18}N_4O_4S_2$ requires C, 51.67; H, 4.30; N, 13.39%).

2-[5-Cyano-2-methylthio-6-(4-pyridyl)pyrimidin-4-yl]amino-5-diethylaminopentane 7. A mixture of **5** (0.2 g, 0.75 mmoles), 4-amino-1-diethylaminopentane (0.2 mL, 1 mmoles), K_2CO_3 (0.3 g, 2.9 mmoles) in 5 mL abs. alcohol was refluxed for 5 hr on steam-bath. It was allowed to cool to room temperature and filtered. The filtrate was evaporated to dryness and crude product crystallized from $CHCl_3$, yield 0.1 g (12%), mp >250°C; MS: m/z 384 (M^+); IR: 2212 (C≡N), 3488 (NH); ^{1}HNMR ($CDCl_3$): 8.77 (d, 2H, Ar–H), 7.82 (d, 2H, Ar–H), 2.59-1.59 (m, 14H, $-SCH_3$, $-(CH_2)_5$, –CH), 1.31 (d, 3H, $-CH_3$), 1.02 (t, 6H, $2CH_3$) (Found: C, 62.37; H, 7.21; N, 21.83. $C_{20}H_{28}N_6S$ requires C, 62.50; H, 7.29; N, 21.87%).

2-Hydrazino-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 8. A mixture of **2a** (0.5 g, 2.04 mmoles) and hydrazine hydrate (6 mL) was heated on steam-bath for 4 hr, allowed to cool and poured on water with vigorous stirring. The solution was neutralized with acetic acid, the precipitate obtained was filtered, washed thoroughly with methanol and dried. It was crystallized from DMF, yield 0.36 g (34%), mp >250°C; MS: m/z 228 (M^+); IR: 1693 (>C=O), 2212 (C≡N), 3282, 3516 (NH, NH_2); ^{1}H NMR (DMSO-d_6): 12.21 (bs, 2H, NH), 11.5 (bs, 2H, NH_2), 8.74 (d, 2H),7.72 (d, 2H, Ar–H) (Found: C, 52.60; H, 3.39; N, 36.79. $C_{10}H_8N_6O$ requires C, 52.63; H, 3.50; N, 36.84%).

6-Cyano-5-oxo-7-(4-pyridyl)-1*H*-1,2,4-triazolo[4,3-*a*]-pyrimidine 9a. A mixture of **8** (0.3 g, 1.5 mmoles) and HCOOH (5 mL) was refluxed for 4 hr in an oil-bath. Excess acid was removed under reduced pressure. Mixture was cooled and poured on water with vigorous stirring. The precipitate obtained was filtered, washed thoroughly with methanol and dried. It was crystallized from DMF, yield 0.36 g (34%), mp >250°C; MS: m/z 238 (M^+); IR: 1693 (>C=O), 2212 (C≡N), 3282 (NH) ^{1}HNMR (DMSO-d_6): 9.35 (s, 1H) 8.74 (d, 2H, Ar–H), 7.72 (d, 2H, Ar–H) (Found: C, 55.40; H, 2.51; N, 35.23. $C_{11}H_6N_6O$ requires C, 55.46; H, 2.52; N, 35.29%).

6-Cyano-3-methyl-5-oxo-7-(4-pyridyl)-1*H*-1,2,4-triazolo[4,3-*a*]pyrimidine 9b. A mixture of **8** (0.3 g, 1.5 mmoles) and CH_3COOH (5 mL) was refluxed in

an oil-bath for 6 hr and then allowed to cool to room temperature. The precipitate thus obtained was filtered, dried and crystallized from DMF, yield 0.13 g (53%), mp >250°C; MS: m/z 252 (M^+); IR: 1649 (>C=O), 2214 (C≡N) and 3323 (NH); ^{1}H NMR (DMSO-d_6): 10.10 (s, H, –NH), 8.78 (d, 2H, Ar–H), 7.71 (d, 2H, Ar–H), 1.92 (s, 3H, $-CH_3$) (Found: C, 57.07; H, 3.04; N, 33.25. $C_{12}H_8N_6O$ requires C, 57.14; H, 3.17; N, 33.33%).

2-(3-Amino-4-carboethoxypyrazol-1-yl)-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 10a. A mixture of **8** (0.3 g, 1.5 mmoles) and ethyl ethoxymethylene cyanoacetate (0.25 g, 1.45 mmoles) in DMF (8 mL) was refluxed in an oil-bath for 4 hr. The precipitate thus obtained was filtered, dried and crystallized from DMF, yield 0.3 g (23%), mp >250°C; MS: m/z 351 (M^+); IR: 1697 (>C=O), 2218 (C≡N) and 3334, 3454 (NH_2); ^{1}HNMR(DMSO-d_6): 12.15 (bs, 1H, NH), 8.92 (d, 2H, Ar–H), 8.03 (s, H, –CH), 7.93 (d, 2H, Ar–H), 7.82 (d, 2H, NH_2), 4.30 (q, 2H, $-CH_2$), 1.35 (t, 3H, $-CH_3$) (Found: C, 54.96; H, 3.48; N, 27.62. $C_{16}H_{13}N_7O_3$ requires C, 54.70; H, 3.70; N, 27.92%).

2-(3-Amino-4-carboethoxy-5-methylthiopyrazol-1-yl)-4-oxo-6-(4-pyridyl)-3,4-dihydropyrimidine-5-carbonitrile 10b. A mixture of **8** (0.3 g, 1.5 mmoles) and ethyl 2-cyano-3,3′-dimethylthioacrylate (0.32 g, 1.4 mmoles) in DMF (8 mL) was heated on steam-bath for 4 hr. The precipitate obtained was filtered, dried and crystallized from $CHCl_3$, yield 0.1 g (68%), mp >250°C; MS: m/z 397 (M^+); IR: 1681 (>C=O), 2224 (C≡N), 3305, 3415 (NH_2) and 3225 (NH); ^{1}H NMR ($CDCl_3$): 12.12 (bs, 1H, NH), 8.81 (d, 2H, Ar–H), 7.79 (bs, 2H, NH_2), 7.80 (d, 2H, Ar–H), 4.20 (q, 2H, $-CH_2$), 2.51 (S, 3H, $-CH_3$), 1.27 (t, 3H, $-CH_3$) (Found: C, 51.69; H, 3.90; N, 24.32. $C_{17}H_{15}N_7O_3S$ requires C, 51.38; H, 3.77; N, 24.68%).

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