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**RESEARCH ARTICLE**

# β-Aminocrotononitrile in heterocyclic synthesis: synthesis of polysubstituted pyridines as precursors to bicycles and polycycles

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β-aminocrotononitrile (**1**) reacted with either cyanothioacetamide to give (**3**) or malononitrile to afford an anion (**5**). Pyridine-2(1*H*)-thione (**4**) was obtained by boiling of (**3**) in ethanol and $Et_3N$ or treatment of (**5**) with $H_2S$, respectively. The reaction of anion **5** with isothiocyanates (**6**) gave *N*-substituted pyridine-2(1*H*)-thiones (**7**). N-Substituted pyridine-2(1*H*)-thiones (**7**) can be used for the preparation of pyrido[2,3-d]pyrimidines (**8a–e**) and (**10a–e**), or the preparation of pyrido[1,2-a]pyrimidines (**12a–d**). 1,8-Naphthyridine derivatives (**14a–d**) and (**16a–e**) can also be obtained from pyridine-2(1*H*)-thione (**7**). Finally, 1,8-naphthyridine derivatives (**16a–e**) can be used for the preparation of tetracyclic compounds **17a–c** and **18a,b**.

*Keywords*: β-Aminocrotononitrile; Pyridinethiones; Pyridopyrimidines; 1,8-Naphthyridines; Malononitrile; Hydrazinolysis

## 1. Introduction

Interest in the development of efficient synthetic approaches for the preparation of functionalized 3-cyano-2(1*H*)-pyridinethiones is related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides and other biologically active compounds [2–4]. The considerable activity of polyfunctionally substituted pyridines [5–7] as calcium channel blockers and as antiviral agent has stimulated considerable interest in the synthesis of pyridines derivatives [8–14]. We have reported [1] that pyridin-2(1*H*)-thione (**4**) was obtained in a very good yield by the reaction of ammonium 1,1,3-tricyano-2-methylprop-2-enide [15] (**5**) with $H_2S$.

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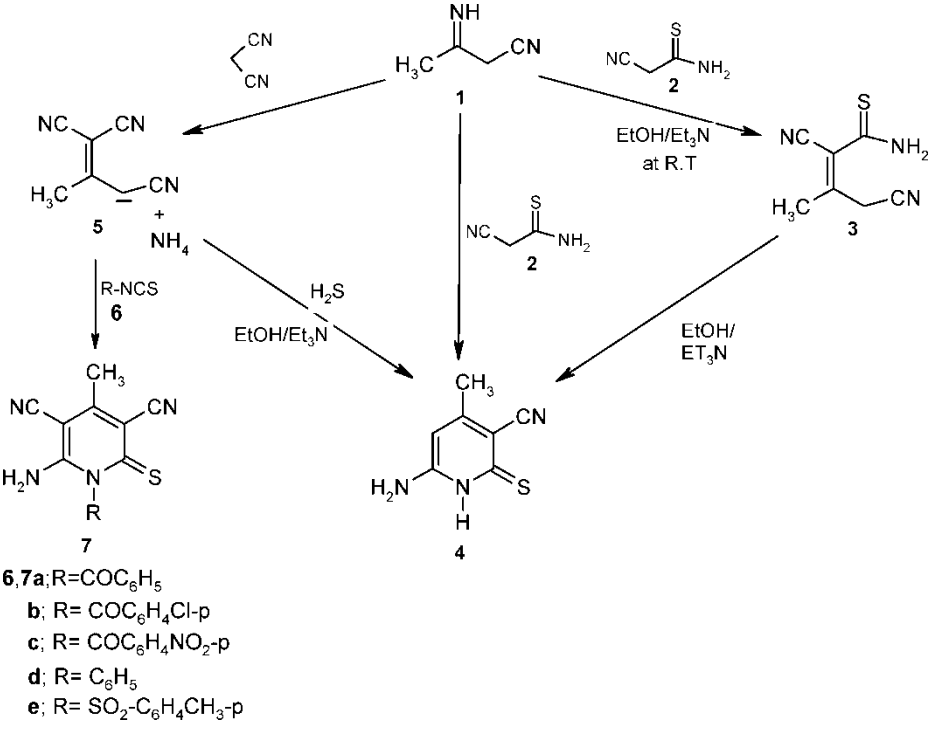
## 2. Results and discussion

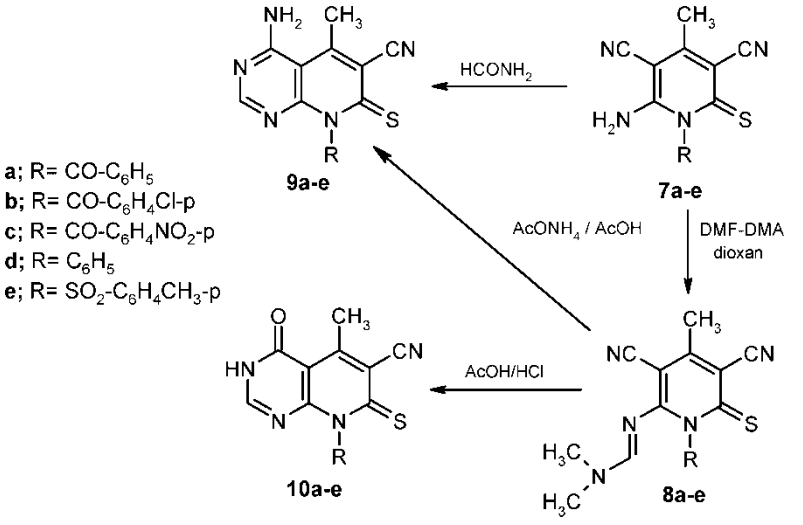
In extending our studies on the synthesis of pyridin-2(1*H*)-thione (**4**), we have found that $\beta$-aminocrotononitrile (**1**) reacted with cyanothioacetamide (**2**) in ethanolic triethylamine at room temperature over seven days to afford the product **3**. The $^1$H NMR of compound **3** revealed a singlet signal at $\delta$ 5.88 ppm for two protons of the methylene group and a deuterable signal at $\delta$ 7.32 ppmassigned to the $NH_2$. The IR spectrum shows the presence of two cyano groups at $\upsilon_{max}$ - 2190 and 2205. Compound **3** was boiled in ethanolic triethylamine to give the pyridin-2(1*H*)-thione (**4**) which can also be obtained by direct reaction of $\beta$-aminocrotononitrile (**1**) with cyanothioacetamide (**2**) in boiling ethanolic triethylamine as outlined in scheme (**1**). N-substituted pyridinethiones (**7a–e**) were obtained by the reaction of ammonium 1,1,3-tricyano-2-methylprop-2-enide [15] (**5**) with isothiocyanate derivatives **6a–e** in very good yield. The IR spectrum shows the appearance of two cyano groups near $\upsilon_{max}$ 2205 in addition to $NH_2$ stretching at $\upsilon_{max}$ 3315, 3165 (scheme 1).




**6**,**7a**;R=$COC_6H_5$
**b**; R= $COC_6H_4Cl$-p
**c**; R= $COC_6H_4NO_2$-p
**d**; R= $C_6H_5$
**e**; R= $SO_2$-$C_6H_4CH_3$-p

SCHEME 1

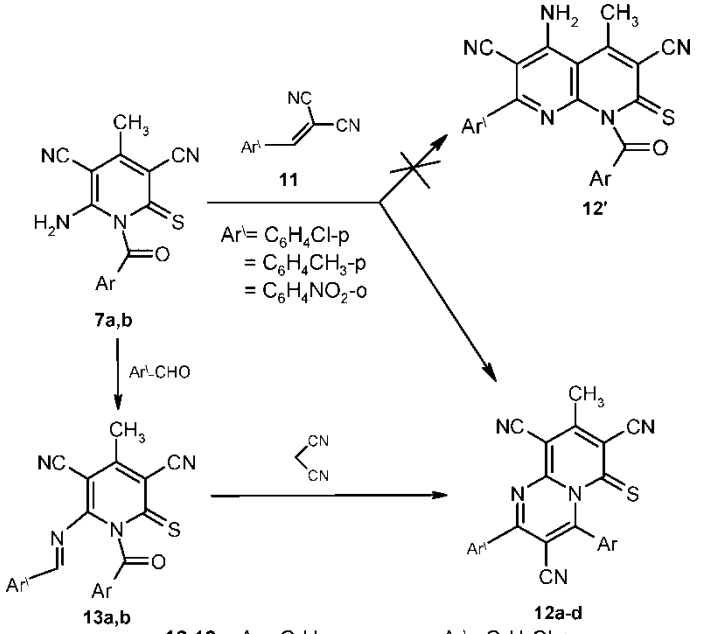
Compounds **7a–e** were boiled in formamide solution to give pyrido[2,3-d]pyrimidines **9a–e**. The $^1$H NMR spectra of compounds **9a–e** exhibited a singlet at $\delta$ 8.19 ppm assigned to the pyrimidine proton and the appearance of an amino proton at $\delta$ 8.21 ppm. Compounds **9a–e** can also be obtained by another synthetic route *via* the condensation of pyidinethiones **7a–e** with N,N-dimethylformamide dimethyl acetal in refluxing dioxane to give compounds **8a–e**, followed by treatment with ammonium acetate in acetic acid. Also, pyrido[2,3-d]pyrimidines **10a–e** were synthesized by boiling of pyridine-2(1*H*)-thiones (**8a–e**) in a mixture of hydrochloric acid and acetic acid (1:3). The $^1$H NMR spectrum shows a doublet at $\delta$ 8.1 ppm assigned to pyrimidine proton and deuterable signal at $\delta$ 13.50 ppm assigned to NH group (scheme 2).



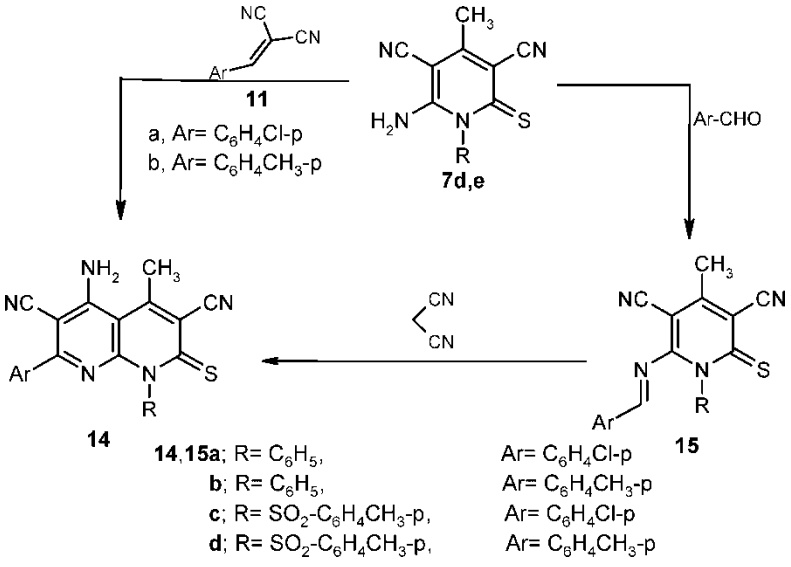

SCHEME 2



Pyridinethiones **7a,b** were reacted with arylidenemalononitriles (**11**) to give products assiogned as either pyrido[1,2-a]pyrimidines **12a–d** or 1,8-naphthyridines (**12′**). The IR spectra show the disappearance of the amino group and the N-substituted carbonyl group confirming that the product is pyrido[1,2-a]pyrimidines **12a–d** not 1,8-naphthyridines (**12′**). For further




SCHEME 3

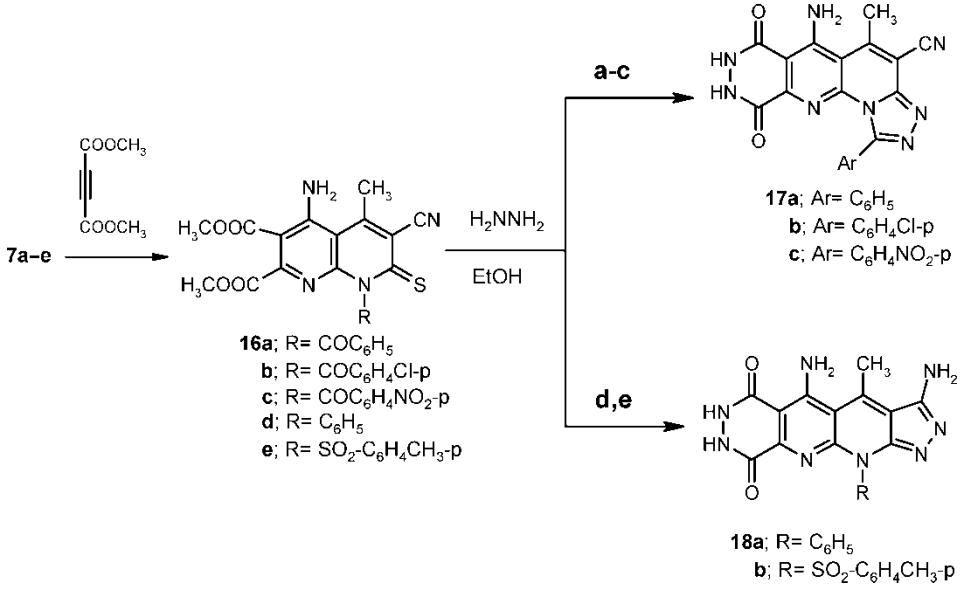



SCHEME 4



confirmation, pyrido[1,2-a]pyrimidines **12a–d** can also be obtained by the condensation of amino group in compound (**7a**) with aromatic aldehydes, which afforded the Schiff's base (**13a,b**) [15] followed by the reaction with malononitrile (scheme 3).

Pyridinethiones **7d,e** were reacted with arylidenemalononitriles **11a,b** to yield 1,8-naphthyridine derivatives **14a–d**. The structures of these compounds (**14a–d**) were confirmed by spectroscopic methods and elemental analysis. Also compound (**14a**) can be obtained by the reaction of compound **7a** with p-chlorobenzaldehyde to afford the Schiff's base (**15a**) [15] followed by the reaction with malononitrile (scheme 4).




SCHEME 5

The structure of 1,8-naphthyridine derivatives **14a–d** was established by spectral data and elemental analysis. Also 1,8-naphthyridine derivatives can also be obtained by the reaction of pyridine-2(1*H*)-thiones **7a–e** with dimethylacetylenedicarboxylate in dimethyl sulfoxide in the presence of potassium carbonate affording 1,8-naphthyridine derivatives **16a–e**, respectively. IR spectra of compounds **16a–e** show the appearance of a peak at $\upsilon_{max}$ 1735 $cm^{-1}$ for the ester carbonyl group, and the $^1H$ NMR spectra show the presence of a singlet signal for six protons at δ 3.7 ppm assigned to two $OCH_3$ groups. When 1,8-naphthyridine derivatives **16a–e** were allowed to react with an excess of hydrazine hydrate in ethanol, the tetracyclic compounds **17a–c** and **18a,b**, both containing an uncommon ring system [16] were obtained (scheme 5). The structures of **17a–c** were confirmed by IR spectra which showed the disappearance of the N-substituted carbonyl as well as the ester carbonyl and the presence of cyano group at $\upsilon_{max}$ 2214 $cm^{-1}$. The structures of **18a,b** were also confirmed by IR spectroscopy which showed the disappearance of the cyano group as well as the ester carbonyl group.

## 3. Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 200 MHz for solutions of [$^2H_6$]dimethyl sulfoxide with tetramethylsilane (TMS) as an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometer using electron impact (EI).



### 3.1 *Preparation of 1,3-dicyano-2-methyl-1-thiocarboxamido-prop-2-ene (3)*

A mixture of β-aminocrotononitrile (**1**) (0.01 mole) and cyanothioacetamide (**2**) (0.01 mole) in ethanol (50 ml) was treated with a small amount of triethylamine. The reaction mixture was left at room temperature for seven days. The solid precipitate so formed was collected by filtration and recrystallized from ethanol as yellow crystals; yield 46%, mp 247–249 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3450, 3350 ($NH_2$) 2205, 2190 (2CN), $\delta_H$(DMSO); 2.16 (s, 3H, $CH_3$), 5.88 (s, 2H, $CH_2$), 7.33 (br. exch., 2H, $NH_2$), MS: m/z (EI) 165 ($M^+$, 100%). Anal. Calcd for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43; S, 19.41. Found: C, 50.79; H, 4.23; N, 25.35; S, 19.38%.

### 3.2 *Preparation of 6-amino-3-cyano-4-methylpyridine-2(1H)-thione (4)*

**3.2.1 Method A.** A solution of compound **3** (0.01 mole) in ethanol (20 ml) was treated with a few drops of triethylamine and heated under reflux for 3 hours. The solid product so formed was filtered off, washed with ethanol and recrystallized from ethanol as orange crystals; yield 72%, mp 258–260 °C (Lit. [1] mp 260 °C).

**3.2.2 Method B.** A mixture of β-aminocrotononitrile (**1**) (0.01 mole) and cyanothioacetamide (**2**) (0.01 mole) in ethanol (50 ml) was treated with few drops of piperidine and refluxed for 3 hours. The solid product so formed was collected by filtration and recrystallized from ethanol.

### 3.3 *Preparation of compounds 7a–e*

**3.3.1 General procedure.** To a solution of ammoniun 1,1,3-tricyano-2-methylprop-2-enide (**5**) (0.01 mole, 1.48 gm) in dry acetone was added with stirring the isothiocyanate

derivative (**6a–e**) (0.01 mole) (which prepared in situ by the reaction of ammonium thiocyanate with the proper aroyl chloride or sulphonyl chloride in dry acetone under reflux for 5 min.) at room temperature for 2 hrs. The solid product so formed was collected by filtration and recrystallized from the proper solvent.

**3.3.2 6-Amino-1-benzoyl-4-methyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (7a).** Compound **7a** was obtained as yellow crystals from acetic acid; yield 54%; mp 243–245 °C (Lit. [15] mp 245 °C). IR: ($\upsilon_{max}$, $cm^{-1}$) 3315, 3165 ($NH_2$), 2205 (CN), 1646 (CON), $\delta_H$(DMSO); 2.55 (s, 3H, $CH_3$), 6.8–7.5 (m, 5H, Ar), 9.5 (br. exch., 2H, $NH_2$).

**3.3.3 6-Amino-1-(4-chlorobenzoyl)-4-methyl-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (7b).** Compound **7b** was obtained as yellow crystals from acetic acid; yield 45.6%; mp 298–300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3315, 3165 ($NH_2$), 2205 (CN), 1646 (CON), $\delta_H$(DMSO); 2.6 (s, 3H, $CH_3$), 7.56, 7.61 (d, 2H, AB), 814, 818 (d, 2H, AB), 9.7 (br. exch., 2H, $NH_2$). Anal. Calcd for $C_{15}H_9ClN_4OS$: C, 54.80; H, 2.76; N, 17.04; S, 9.75. Found: C, 54.76; H, 2.69; N, 16.98; S, 9.67%.



**3.3.4 6-Amino-4-methyl-1-(4-nitrobenzoyl)-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (7c).** Compound **7c** was obtained as orange crystals from acetic acid; yield 56%, mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3315, 3165 ($NH_2$), 2215 (CN), 1645 (CON), $\delta_H$(DMSO); 2.58 (s, 3H, $CH_3$), 8,31 (s, 4H, Ar), (br. exch., 2H, $NH_2$). Anal. Calcd for $C_{15}H_9N_5O_3S$: C, 53.09; H, 2.67; N, 20.64; S, 9.45. Found: C, 53.02; H, 2.59; N, 20.58; S, 9.37%.

**3.3.5 Preparation of 6-amino-4-methyl-1-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (7d).** To a solution of ammonium 1,1,3-tricyano-2-methylprop-2-enide (**5**) (0.01 mole, 1.48 gm) in dry acetone was added the phenyl isothiocyanate. The reaction mixture was refluxed for one hour. The solid product so formed was collected by filtration and recrystallized from ethanol as brown crytals; yield 37%; mp 183–185 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3315, 3165 ($NH_2$), 2210 (CN), $\delta_H$(DMSO); 2.46 (s, 3H, $CH_3$), 6.88–7.6 (m, 5H, Ar), 8.88 (br. exch., 2H, $NH_2$). Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04; S, 12.04. Found: C, 63.10; H, 3.74; N, 21.00; S, 12.01%.

**3.3.6 6-Amino-4-methyl-1-(4-methylbenzenesulfonyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbo-nitrile (7e).** Compound **7e** was obtained as brown crystals from acetic acid, yield 56.98%, mp 258–260 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3417, 3309 ($NH_2$), 2214 (CN), $\delta_H$(DMSO); 2.57 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 7.54 (d, 2H, AB, $J = 11$ Hz), 7.9 (d, 2H, AB, $J = 11$ Hz), 9.3 (br. exch., 2H, $NH_2$). Anal. Calcd for $C_{15}H_{12}N_4O_2S_2$: C, 52.31; H, 3.51; N, 16.27; S, 18.62. Found: C, 52.28; H, 3.47; N, 16.19; S, 18.56%.

### 3.4 *Reaction of compounds (7a–e) with dimethylformamidedimethylacetal [DMFDMA]*

**3.4.1 General procedure.** A mixture of any one of compounds **7a–e** (0.01 mole) and *N,N*-dimethylformamide dimethyl acetal [DMFDMA] in dry dioxane was refluxed for two hours. The solvent was evaporated under vacuo and the solid product so formed was collected by filtration and recrystallized from the proper solvent.

**3.4.2 1-Benzoyl-6-(*N,N*-dimethylformimdyl)-4-methyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbo-nitrile (8a).** Compound **8a** was obtained as brown crystals from ethanol; yield 78.6%; mp 228–230 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2210 (CN), $\delta_H$ (DMSO) 2.63 (s, 3H, $CH_3$), 3.33 (s, 6H, $2CH_3$), 7.49–7.64 (m, 3H, Ar), 8.19–8.2 (d, 2H, Ar), 8.54 (s, 1H, CH). Anal. Calcd for $C_{18}H_{15}N_5OS$: C, 61.87; H, 4.33; N, 20.04; S, 9.18. Found: C, 61.84; H, 4.27; N, 20.00; S 9.12%.

**3.4.3 1-(4-Chlorobenzoyl)-6-(*N,N*-dimethylformimdyl)-4-methyl-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8b).** Compound **8b** was obtained as brown crystals from ethanol; yield 81.37%; mp 250–252 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2210 (CN), $\delta_H$ (DMSO) 2.64 (s, 3H, $CH_3$), 3.36 (s, 6H, $2CH_3$), 7.58, 7.61 (d, 2H, AB), 8.15, 8.18 (d, 2H, AB), 8.55 (s, 1H, CH). Anal. Calcd for $C_{18}H_{14}ClN_5OS$: C, 56.32; H, 3.68; N, 18.24; S, 8.35. Found: C, 56.28; H, 3.62; N, 18.18; S 8.20%.

**3.4.4 6-(*N,N*-Dimethylformimdyl)-4-methyl-1-(4-nitrobenzoyl)-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8c).** Compound **8c** was obtained as brown crystals from ethanol; yield 76.48%; mp 244–246 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2210 (CN), $\delta_H$ (DMSO); 2.7 (s,3H,$CH_3$), 3.4 (s,6H,$2CH_3$), 8.5 (s,1H,CH), 7.7 (d,2H,AB), 8.9 (d,2H,AB). Anal. Calcd for $C_{18}H_{14}N_6O_3S$: C, 54.82; H, 3.58; N, 21.31; S, 8.13. Found: C, 54.77; H, 3.54; N, 21.26; S 8.07%.

**3.4.5 6-(*N,N*-Dimethylformimdyl)-4-methyl-1-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbo-nitrile (8d).** Compound **8d** was obtained as reddish brown crystals from ethanol; yield 79.18%; mp 214–216 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2200 (CN), $\delta_H$(DMSO); 2.72 (s, 3H, $CH_3$), 3.38 (s, 6H, $2CH_3$), 7.46–8.01 (m, 5H, Ar), 8.5 (s, 1H, CH). Anal. Calcd for $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70; N, 21.79; S, 9.98. Found: C, 63.47; H, 4.65; N, 21.75; S, 9.93%.

**3.4.6 6-(*N,N*-Dimethylformimdyl)-4-methyl-1-(4-methylbenzene-sulfonyl)-1-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (8e).** Compound **8e** was obtained as brown crystals from ethanol; yield 70.18%; mp 146–147 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2210 (CN), $\delta_H$(DMSO); 2.35 (s, 3H, $CH_3$), 2.72 (s, 3H, $CH_3$), 8.34 (d, 2H, AB, $J = 12$ Hz), 8.8 (d, 2H, AB, $J = 12$ Hz), 8.52 (s, 1H, CH). Anal. Calcd for $C_{18}H_{17}N_5O_2S_2$: C, 54.12; H, 4.29; N, 17.53; S, 16.05. Found: C, 54.07; H, 4.25; N, 17.48; S, 16.01%.

### 3.5 *Preparation of pyrido[2,3-d]pyrimidine derivatives (9a–e)*

**3.5.1 Method A.** A mixture of **8a–e** (0.01 mole) and ammonium acetate (0.03 mole) in acetic acid (10 ml) was refluxed for 3 hours. The precipitate so formed after cooling was collected by filtration and recrystallized from the proper solvent.

**3.5.2 Method B.** A mixture of **7a–e** (0.01 mole) and formamide was left under reflux for 2 hours.

**3.5.3 4-Amino-8-benzoyl-5-methyl-7-thioxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (9a).** Compound **9a** was obtained as brown crystals from acetic acid; yield 43.47%; mp 268–270 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3330, 3180 ($NH_2$), 2210 (CN), 1645 (CO)

$\delta_H$(DMSO) 2.6 (s, 3H, $CH_3$), 7.52–7.61 (m+br. exch., 5H, $NH_2$, Ar), 8.19–8.21 (d, 2H, Ar). Anal. Calcd for $C_{16}H_{11}N_5OS$: C, 59.80; H, 3.45; N,21. 79; S, 9.98. Found: C, 59.76; H, 3.38; N, 21.73; S, 9.92%.

**3.5.4 4-Amino-8-(4-chlorobenzoyl)-5-methyl-7-thioxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (9b).** Compound **9b** was obtained as yellow crystals from acetic acid; yield 54.34%; mp 304–306 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3310, 3180 ($NH_2$), 2205 (CN), 1645 (CO), $\delta_H$ (DMSO); 2.63 (s, 3H, $CH_3$), 7.6 (br. exch., 2H, $NH_2$), 8.31 (s, 1H, ring-H), 8.46 (d, 2H, AB, $J = 11$ Hz), 8.9 (d, 2H, AB, $J = 11$ Hz). Anal. Calcd for $C_{16}H_{10}ClN_5OS$: C, 54.01; H, 2.83; N, 19.68; S, 9.01. Found: C, 53.97; H, 2.76; N, 19.62; S, 8.97%.

**3.5.5 4-Amino-5-methyl-8-(4-nitrobenzoyl)-7-thioxo-7,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (9c).** Compound **9c** was obtained as orange crystals from acetic acid; yield 52%; mp 290–292 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3315, 3150 ($NH_2$), 2215 (CN), 1650 (CO), $\delta_H$ (DMSO); 2.65 (s, 3H, $CH_3$), 7.8 (br. exch., 2H, $NH_2$), 8.4 (s, 1H, CH), 9.27 (d, 2H, AB, $J = 12$ Hz), 9.37 (d, 2H, AB, $J = 12$ Hz). Anal. Calcd for $C_{16}H_{10}N_6O_3S$: C, 52.46; H, 2.75; N, 22.94; S, 8.75. Found: C, 52.41; H, 2.72; N, 22.87; S, 8.72%).



**3.5.6 4-Amino-5-methyl-8-phenyl-7-thioxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (9d).** Compound **9d** was obtained as orange crystals from acetic acid; yield 54.34%; mp 272–274 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3200 ($NH_2$), 2205 (CN), $\delta_H$(DMSO) 2.46 (s, 3H, $CH_3$), 7.26–7.64 (m, 6H, Ar), 7.89 (br. exch., 2H, $NH_2$). Anal. Calcd for $C_{15}H_{11}ClN_5S$: C, 61.42; H, 3.78; N, 23.87; S, 10.93. Found: C, 61.35; H, 3.72; N, 23.83; S, 10.85%.

**3.5.7 4-Amino-5-methyl-8-(4-methylbenzenesulfonyl)-7-thioxo-7,8-dihydropyrido [2,3-d]-pyrimidine-6-carbonitrile (9e).** Compound **9e** was obtained as brown crystals from acetic acid; yield 51.3%; mp 248–250 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3330, 3184 ($NH_2$), 2214 (CN), $\delta_H$ (DMSO); 2.35 (s, 3H, $CH_3$), 2.61 (s, 3H, $CH_3$), 7.72 (br. exch., 2H, $NH_2$), 8.32 (s, 1H, CH), 7.9 (d, 2H, AB), 8.38 (d, 2H, AB). Anal. Calcd for $C_{16}H_{13}N_5O_2S_2$: C, 51.74; H, 3.53; N, 18.85; S, 17.26. Found: C, 51.68; H, 3.48; N, 18.81; S, 17.22%.

### 3.6 *Preparation of pyrido[2,3-d]pyrimidine derivatives (10a–e)*

**3.6.1 General procedure.** Compounds **8a–e** were dissolved in a mixture of acetic acid/hydrochloric acid (3:1) (20 ml). The reaction mixture was refluxed for two hours. The precipitate so formed on cooling was collected by filtration and recrystallized from the proper solvent.

**3.6.2 8-Benzoyl-5-methyl-4-oxo-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbo-nitrile (10a).** Compound **10a** was obtained as yellow crystals from acetic acid; yield 32.6%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3450 (NH), 1645 (CO), $\delta_H$ (DMSO) 2.94 (s,3H,$CH_3$), 7.57–7.71 (m, 5H, Ar), 8.15–8.18 (d, 2H, Ar), 13.43 (br. exch., 1H, NH). MS (EI) m/z: 321 (3.1%). Anal. Calcd for $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38; S, 9.95. Found: C, 59.57; H, 3.07; N, 17.32; S, 9.91%.

**3.6.3 8-(4-Chlorobenzoyl)-5-methyl-4-oxo-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (10b).** Compound **10b** was obtained as yellow crystals from

acetic acid; yield 50.3%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3350 (NH), 2215 (CN), 1650 (CO), $\delta_H$ (DMSO) 2.98 (s, 3H, $CH_3$), 7.57, 7.62 (d, 2H, AB), 7.95, 8.00 (d, 1H, CH, Ar), 8.20, 8.25 (d, 2H, AB), 13.45 (br. exch., 1H, NH). Anal. Calcd for $C_{16}H_9ClN_4O_2S$: C, 53.86; H, 2.54; N, 15.70; S, 8.99. Found: C, 53.81; H, 2.48; N, 15.64; S, 8.93%.

**3.6.4 5-Methyl-8-( 4-Nitrobenzoyl )-4-oxo-7-thioxo-3,4,7,8-tetrahydropyrido[ 2,3-d ] pyrimidine-6-carbonitrile (10c).** Compound **10c** was obtained as red crystals from acetic acid; yield 42.5%; mp 306–308 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3450 (NH), 2210 (CN), $\delta_H$(DMSO); 2.81 (s, 3H, $CH_3$), 8.25 (s, 1H, CH), 9.21 (d, 2H, AB), 9.37 (d, 2H, AB), 13.43 (br. exch., 1H, NH). Anal. Calcd for $C_{16}H_9N_5O_4S$: C, 52.32; H, 2.47; N, 19.06; S, 8.73. Found: C, 52.28; H, 2.41; N, 19.02; S, 8.67%.

**3.6.5 5-Methyl-4-oxo-8-phenyl-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbo-nitrile (10d).** Compound **10d** was obtained as yellow crystals from acetic acid; yield 21.7%; mp 236–238 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3200 (NH), 2205 (CN). $\delta_H$(DMSO); 2.78 (s, 3H, $CH_3$), 7.46–8.01 (m, 5H, Ar), 8.5 (s, 1H, CH), 13.43 (br. exch., 1H, NH). MS(EI), m/z 294 (0.6%), m/z 266 (35%), m/z 238 (100%). Anal. Calcd for $C_{15}H_{10}N_4OS$: C, 61.21; H, 3.42; N, 19.03; S, 10.89. Found: C, 61.15; H, 3.35; N, 18.98; S, 10.83%.

**3.6.6 5-Methyl-8-(4-methylbenzenesulfonyl)-4-oxo-7-thioxo-3,4,7,8-tetrahydropyrido [2,3-d]-pyrimi dine-6-carbonitrile (10e).** Compound **10e** was obtained as brown crystals from acetic acid; yield 42.6%; mp 244–246 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3330 (NH), 2214 (CN), $\delta_H$ (DMSO); 2.76 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 8.34 (d, 2H, AB), 8.32 (s, 1H, CH), 8.81 (d, 2H, AB), 13.41 (br. exch., 1H, NH). Anal. Calcd for $C_{16}H_{12}N_4O_3S_2$: C, 51.60; H, 3.25; N, 15.04; S, 17.22. Found: C, 51.55; H, 3.22; N, 15.00; S, 17.18%.



### 3.7 *Reaction of (7a,b) and (7d,e) with arylidenemalononitrile (11)*

**3.7.1 Method A.** To a solution of any one of compounds **7a,b** and **7d,e** (0.01 mole) in dry dioxane (20 ml) was added the arylidenemalononitrile (**11**) (0.01 mole) and few drops of pipridine. The reaction mixture was refluxed for four hours, then poured into ice-cold water and acidified by HCl. The solid product so formed was collected by filtration, washed with water several times, dried and recrystallized from the proper solvent.

**3.7.2 Method B.** To a solution of **13** or **15** (0.01 mole) in dry dioxane (20 ml), malononitrile was added. The reaction mixture was treated with little amount of triethylamine, then refluxed for three hours. The solid product so formed was filtered off, washed with ethanol and recrystallized from the proper solvent.

**3.7.3 2-(4-Chlorophenyl)-8-methyl-4-phenyl-6-thioxo-6H-pyrido[1,2-a]pyrimidine-3,7, 9-tri-arbonitrile (12a).** Compound **12a** was obtained as orange crystals from dioxane/ethanol mixture (1:1), yield 81%; mp 222–224 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2225 (CN), $\delta_H$(DMSO); 3.6 (s, 3H, $CH_3$), 7.14–7.6 (m, 9H, Ar). MS (EI) m/z 437 ($M^+$, 41%), 439 ($M^{+2}$, 15%). Anal. Calcd for $C_{24}H_{12}ClN_5S$: C, 65.83; H, 2.76; N, 15.99; S, 7.32. Found: C, 65.75; H, 2.72; N, 15.95; S, 7.27%.

**3.7.4 8-Methyl-4-phenyl-6-thioxo-2-(4-tolyl)-6H-pyrido[1,2-a]pyrimidine-3,7,9-tricarbonitrile (12b).** Compound **12b** was obtained as brown crystals from dioxane/ethanol mixture (1:1); yield 49.3%; mp 208–210 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2223 (CN), $\delta_H$ (DMSO); 3.51 (s, 3H, $CH_3$), 7.1–7.5 (m, 9H, Ar). Anal. Calcd for $C_{25}H_{15}N_5S$: C, 71.92; H, 3.62; N, 16.77; S, 7.68. Found: C, 71.87; H, 3.59; N, 16.73; S, 7.65%.

**3.7.5 4-(4-Chlorophenyl)-8-methyl-6-thioxo-2-(4-tolyl)-6H-pyrido[1,2-a]pyrimidine-3,7,9-tri-arbonitrile (12c).** Compound **12c** was obtained as orange crystals from dioxane/ethanol mixture (1:1); yield 43.48%; mp 260–262 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2226 (CN), $^1$HNMR (DMSO) $\delta_H$ 2.1 (s, 3H, $CH_3$), 3.6 (s, 3H, $CH_3$), 7.38–7.42 (m, 4H, Ar), 7.55, 7.59 (d, 2H, AB), 7.75–7.79 (d, 2H, AB). Anal. Calcd for $C_{25}H_{14}ClN_5S$: C, 66.44; H, 3.12; N, 15.50; S, 7.09. Found: C, 66.38; H, 3.07; N, 15.45; S, 7.06%.

**3.7.6 4-(4-Chlorophenyl)-8-methyl-2-(2-nitrophenyl)-6-thioxo-6H-pyrido[1,2-a]pyrimidine-3,7,9-tricarbonitrile (12d).** Compound **12d** was obtained as brown crystals from dioxane/ethanol mixture (1:1); yield 82.19%; mp 220–222 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 2224 (CN), $\delta_H$(DMSO); 3.6 (s, 3H, $CH_3$), 7.22–8.2 (m, 8H, Ar). Anal. Calcd for $C_{24}H_{11}ClN_6O_2S$: C, 59.69; H, 2.30; N, 17.40; S, 6.64. Found: C, 59.65; H, 2.27; N, 17.36; S, 6.60%.

**3.7.7 5-Amino-7-(4-chlorophenyl)-4-methyl-1-phenyl-2-thioxo-1,2-dihydro[1,8]naphthyridine-3,6-dicarbonitrile (14a).** Compound **14a** was obtained from ethanol as orange crystals; yield 77.4%; mp 314–316 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3346–3220 ($NH_2$), 2210 (CN), $^1$HNMR: $\delta_H$ 2.1 (s, 3H, $CH_3$), 7.11–7.52 (m, 11H, Ar+$NH_2$). Anal. Calcd for $C_{23}H_{14}ClN_5S$: C, 64.56; H, 3.30; N, 16.37; S, 7.49. Found: C, 64.51; H, 3.27; N, 16.33; S, 7.46%.

**3.7.8 5-Amino-4-methyl-1-phenyl-2-thioxo-7-(4-tolyl)-1,2-dihydro[1,8]naphthyridine-3,6-dicarbonitrile (14b).** Compound **14b** was obtained from ethanol as orange crystals; yield 74.3%; mp 276–278 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3733–3649 ($NH_2$), 2210 (CN), $\delta_H$(DMSO); 2.4 (s, 3H, $CH_3$), 2.3 (s, 3H, $CH_3$), 7.1–7.6 (m, 11H, Ar+$NH_2$). Anal. Calcd for $C_{24}H_{17}N_5S$: C, 70.74; H, 4.21; N, 17.19; S, 7.87. Found: C, 70.68; H, 4.17; N, 17.15; S, 7.85%.

**3.7.9 5-Amino-7-(4-chlorophenyl)-4-methyl-1-(4-methylbenzene-sulfonyl)-2-thioxo-1,2-dihydro-1,8] naphthyridine-3,6-dicarbonitrile (14c).** Compound **14c** was obtained from ethanol as brown crystals; yield 68.7%; mp 244–246 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3646–3545 ($NH_2$), 2210 (CN), $\delta_H$ (DMSO); 2.35 (s, 3H, $CH_3$), 2.7 (s, 3H, $CH_3$), 7.34–7.93 (m, 10H, Ar+$NH_2$). Anal. Calcd for $C_{24}H_{16}ClN_5O_2S_2$: C, 56.97; H, 3.19; N, 13.84; S, 12.67. Found: C, 56.93; H, 3.17; N, 13.80; S, 12.64%.

**3.7.10 5-Amino-4-methyl-1-(4-methylbenzenesulfonyl)-2-thioxo-7-(4-tolyl)-1,2-dihydro-[1,8]- naphthyridine-3,6-dicarbonitrile (14d).** Compound **14d** was obtained from ethanol as brown crystals; yield 64.29%; mp 150–152 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3749–3649 ($NH_2$), 2206 (CN) $\delta_H$ (DMSO); 2.33 (s, 3H, $CH_3$), 2.61 (s,3H, $CH_3$), 7.15–7.88 (m, 10H, Ar+$NH_2$). Anal. Calcd for $C_{25}H_{19}N_5O_2S_2$: C, 61.84; H, 3.94; N, 14.42; S, 13.21% Found: C, 61.78; H, 3.92; N, 14.38; S, 13.18%.

### 3.8 *Preparation of compounds (16a–e)*

**3.8.1 General procedure.** A mixture of compound **7a–e** (0.01 mole) and anhydrous potassium carbonate (2 gm) in DMSO (30 ml) were stirred for 10 minutes, (0.01 mole) of dimethylacetylenedicarboxylate in DMSO (5 ml) was added dropwise to the stirred mixture. The stirring was continued for an additional 15 hours at room temperature. The reaction mixture was poured into 200 ml of ice-water and acidified with dilute HCl. The solid obtained was collected by filtration, washed with water several times and recrystallized from the proper solvent.

**3.8.2 4-Amino-8-benzoyl-6-cyano-5-methyl-7-thioxo-7,8-dihydro[1,8]naphthyridine-2, 3-dicaroboxylic acid dimethyl ester (16a).** Compound **16a** was obtained as orange crystals from methanol; yield 64.19%; mp 142–144 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3390, 3201 ($NH_2$), 2214 (CN), 1735 (CO), $^1$HNMR($CDCl_3$): $\delta_H$ 2.55 (s, 3H, $CH_3$), 3.83 (s, 6H, $OCH_3$), 7.57–7.92 (m, 7H, Ar, $NH_2$). Anal. Calcd for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84; S, 7.35. Found: C, 57.76; H, 3.68; N, 12.81; S, 7.33%.



**3.8.3 4-Amino-8-(4-chlorobenzoyl)-6-cyano-5-methyl-7-thioxo-7,8-dihydro[1,8]naphthyridine-2,3- dicaroboxylic acid dimethyl ester (16b).** Compound **16b** was obtained as brown crystals from methanol; yield 55.81%; mp 198–200 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3421, 3200 ($NH_2$), 2216 (CN), 1730 (CO), $\delta_H$(DMSO); 2.7 (s, 3H, $CH_3$), 3.88 (s, 3H, $OCH_3$), 7.45 (d, 2H, AB), 7.61 (br. exch., 2H, $NH_2$), 7.9 (d, 2H, AB). Anal. Calcd for $C_{21}H_{15}ClN_4O_5S$: C, 53.56; H, 3.21; N, 11.90; S, 6.81. Found: C, 53.53; H, 3.20; N, 11.88; S, 6.80%.

**3.8.4 4-Amino-6-cyano-5-methyl-8-(4-nitrobenzoyl)-7-thioxo-7,8-dihydro[1,8]naphthyridine-2,3- dicaroboxylic acid dimethyl ester (16c).** Compound **16c** was obtained as brown crystals from methanol; yield 58.82%; mp 186–188 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3200 ($NH_2$), 2221 (CN), 1735 (CO), $\delta_H$ (DMSO); 2.61 (s, 3H, $CH_3$), 3.88 (s, 3H, $OCH_3$), 7.52 (br. exch., 2H, $NH_2$), 8.21 (d, 2H, AB), 8.37 (d, 2H, AB). Anal. Calcd for $C_{21}H_{15}N_5O_7S$: C, 52.39; H, 3.14; N, 14.55; S, 6.66. Found: C, 52.35; H, 3.11; N, 14.52; S, 6.64%.

**3.8.5 4-Amino-6-cyano-5-methyl-8-phenyl-7-thioxo-7,8-dihydro[1,8]naphthyridine-2, 3- dicaroboxylic acid dimethyl ester (16d).** Compound **16d** was obtained as brown crystals from methanol; yield 72%; mp 140–142 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3178 ($NH_2$), 2214 (CN), 1732 (CO), $\delta_H$ (DMSO); 2.7 (s, 3H, $CH_3$), 2.3 (s, 3H, $CH_3$), 3.8 (s, 3H, $CH_3$), 7.34 (d, 2H, AB), 7.54 (br. exch., 2H, $NH_2$), 7.81 (d, 2H, AB). Anal. Calcd for $C_{20}H_{16}N_4O_4S$: C, 58.81; H, 3.95; N, 13.72; S, 7.85. Found: C, 58.77; H, 3.93; N, 13.70; S, 7.83%.

**3.8.6 4-Amino-6-cyano-5-methyl-7-thioxo-8-(4-tolylsulfonyl)-7,8-dihydro[1,8]naphthyridine-2,3- dicaroboxylic acid dimethyl ester (16e).** Compound **16e** was obtained as brown crystals from methanol; yield 66.14%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3379, 3321 ($NH_2$), 2218 (CN), 1735 (CO), $\delta_H$(DMSO); 2.3 (s, 3H, $CH_3$), 2.71 (s, 3H, $CH_3$), 3.88 (s, 3H, $OCH_3$), 7.34 (d, 2H, AB), 7.6 (br. exch., 2H, $NH_2$), 7.81 (d, 2H, AB). Anal. Calcd for $C_{21}H_{18}N_4O_6S_2$: C, 51.84; H, 3.73; N, 11.52; S, 13.18. Found: C, 51.80; H, 3.71; N, 11.50; S, 13.15%.

### 3.9 *Reaction of compounds (16a–e) with hydrazine hydrate*

**3.9.1 General procedure.** A mixture of compound (**16a–e**) (0.01 mole) and hydrazine hydrate (2 ml) in ethanol (50 ml) were refluxed for 2 hours. The solvent was evaporated under vacum, the solid product so formed was filtered off, washed with ethanol and recrystallized from the proper solvent.

**3.9.2 6-Amino-5-methyl-7,10-dioxo-1-phenyl-7,8,9,10-tetrahydro-2,3,8,9,11,11b-hexaaza-cyclo-enta[a]anthracene-4-carbonitrile (17a).** Compound **17a** was obtained as brown crystals from acetic acid; yield 57%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3150 ($NH_2$), 2210 (CN), 1620 (CONH), $\delta_H$ (DMSO); 2.7 (s, 3H, $CH_3$), 7.3–7.5 (m, 5H, Ar), 7.8 (br. exch., 2H, $NH_2$), 8.1 (d, 1H, NH), 8.18) d, 1H, NH). Anal. Calcd for $C_{19}H_{12}N_8O_2$: C, 59.37; H, 3.15; N, 29.15. Found: C, 59.34; H, 3.13; N, 29.10%.

**3.9.3 6-Amino-1-(4-chlorophenyl)-5-methyl-7,10-dioxo-7,8,9,10-tetrahydro-2,3,8,9,11, 11b-hexaaza-cyclopenta[a]anthracene-4-carbonitrile (17b).** Compound **17b** was obtained as brown crystals from acetic acid; yield 57.7%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3201 ($NH_2$), 2214 (CN), 1620 (CONH), $\delta_H$ (DMSO); 2.51 (s, 3H, $CH_3$), 6.12 (br. exch., 2H, $NH_2$), 7.33 (d, 2H, AB), 7.42 (d, 2H, AB), 8.16 (br. exch., 2H, 2NH). Anal. Calcd for $C_{19}H_{11}ClN_8O_2$: C, 54.49; H, 2.65; N, 26.76. Found: C, 54.45; H, 2.63; N, 26.72%.

**3.9.4 6-Amino-5-methyl-1-(4-nitrophenyl)-7,10-dioxo-7,8,9,10-tetrahydro-2,3,8,9,11, 11bhexaaza-cyclopenta[a]anthracene-4-carbonitrile (17c).** Compound **17c** was obtained as brown crystals from acetic acid; yield 67.26%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3310, 3209 ($NH_2$), 2214 (CN), 1620 (CONH), $\delta_H$ (DMSO); 2.46 (s, 3H, $CH_3$), 7.5 (br. exch., 2H, $NH_2$), 7.7 (d, 2H, AB), 8.1 (br. exch., 2H, 2NH), 8.3 (d, 2H, AB). Anal. Calcd for $C_{19}H_{11}N_9O_4$: C, 53.15; H, 2.58; N, 29.36. Found: C, 53.11; H, 2.57; N, 29.32%.

**3.9.5 3,5-Diamino-4-methyl-11-phenyl-7,8-dihydro-11H-1,2,7,8,10,11-hexaaza-cyclo-penta[b]anthra- cene-6,9-dione (18a).** Compound **18a** was obtained as brown crystals from acetic acid; yield 72.73%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3300, 3200 ($NH_2$, NH), 1620 (CO). Anal. Calcd for $C_{18}H_{14}N_8O_2$: C, 57.75; H, 3.77; N, 29.93. Found: C, 57.70; H, 3.75; N, 29.90%.

**3.9.6 3,5-Diamino-4-methyl-11-(4-tolylsulfonyl)-7,8-dihydro-11H-1,2,7,8,10,11-hexaaza-cyclopenta-[b]anthracene-6,9-dione (18b).** Compound **18b** was obtained as brown cystals from acetic acid; yield 65.79%; mp > 300 °C. IR: ($\upsilon_{max}$, $cm^{-1}$) 3350, 3201 ($NH_2$, NH), 1612 (CONH). Anal. Calcd for $C_{19}H_{16}N_8O_4S$: C, 50.44; H, 3.56; N, 24.77; S, 7.09. Found: C, 50.40; H, 3.54; N, 24.73; S, 7.07%.

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