

2-HALOALKYLIDENEPROPANEDINITRILES IN THE SYNTHESIS OF FUSED PYRIMIDINES

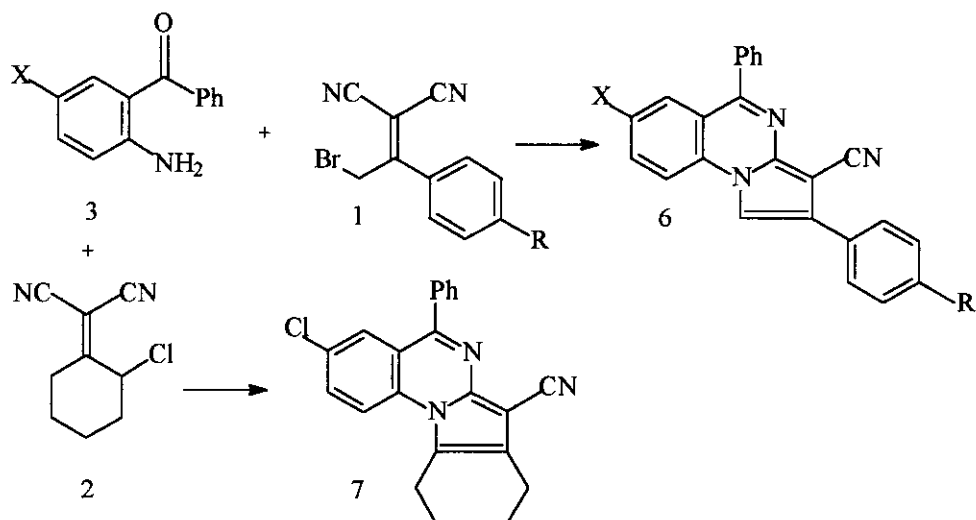
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Abstract - A single step synthesis of various heterocycles such as 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (**6**), 5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (**7**), 2-cyanocyclopenta[4,5]thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-ones (**9**) and 4-(2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (**10**) have been reported using 2-haloalkylidenepropanedinitriles (**1**) and (**2**) with 5-substituted 2-aminobenzophenones (**3**), 2-amino-3-carbethoxycyclopenta[4,5]thiophenes (**4**) and 3-substituted 4-amino-5-carbethoxythiazole-2-thiones (**5**) respectively.

o-Aminonitriles, the readily accessible building blocks for the construction of many important heterocycles, have been prepared using 2-haloalkylidenepropanedinitriles under Gewald conditions.¹⁻³ Moreover, a variety of heterocyclic ring systems including pyrroloimidazole,⁴ thiazole,⁵ thiazepine,⁶ pyrroloquinazoline,⁷⁻⁹ and pyrrolothienopyrimidines^{9,10} have been reported using 2-haloalkylidenepropanedinitriles. Herein, we wish to report the synthesis of 1,7-disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (**6**), 3-chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (**7**), 1-substituted 2-cyanocyclopenta[4,5]thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-ones (**9**), and 3-substituted 4-(1-substituted 2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (**10**) in order to establish the utility and versatility of 2-haloalkylidenepropanedinitriles (**1**) and (**2**).

Treatment of 5-substituted 2-aminobenzophenones (**3**) with 2-bromoalkylidenepropanedinitriles (**1**) in propanol at 65-70°C afforded 1,7-disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (**6**). Analogous treatment of **3** with 2-chlorocyclohexalidenepropanedinitrile (**2**) yielded 3-chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (**7**) (Scheme 1).

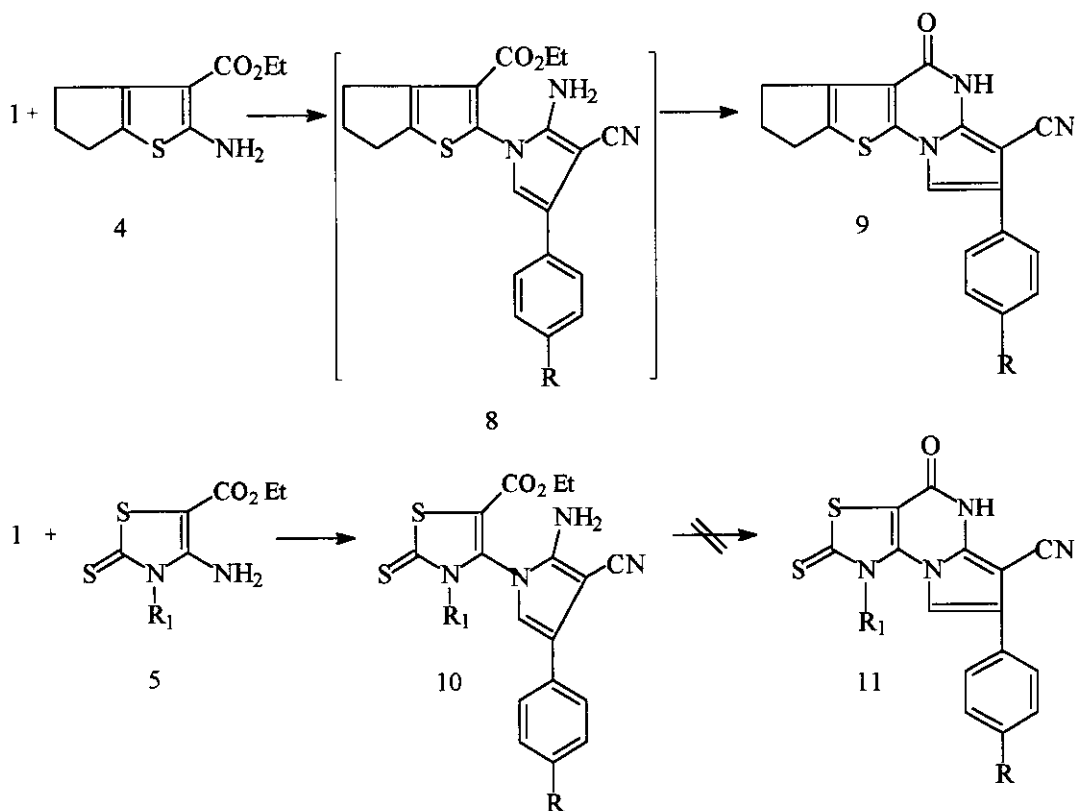


Scheme 1

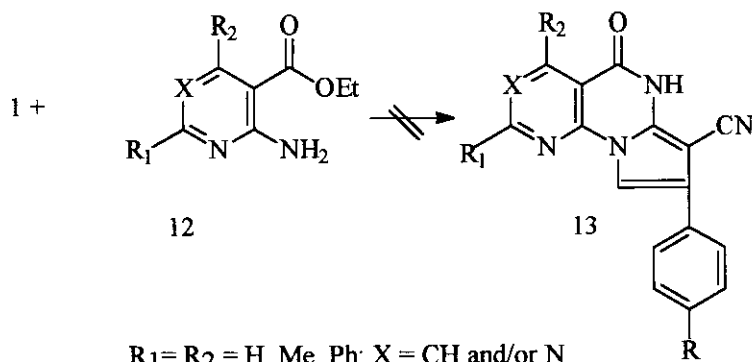
UV(methylene chloride) spectra of compounds (**6**) and (**7**) exhibited two prominent λ_{max} in the region 246-393 nm. A sharp characteristic band for $\text{C}\equiv\text{N}$ near 2200 cm^{-1} was found in IR(KBr) spectra of compounds (**6**) and (**7**) along with the absorptions in the region $1596\text{-}1484\text{ cm}^{-1}$ ($\text{C}=\text{C}$, $\text{C}=\text{N}$). The absence of absorptions due to amino and carbonyl groups near $3400\text{-}3200$ and 1700 cm^{-1} respectively proved the formation of tricyclic products (**6**) and (**7**). $^1\text{H NMR}$ (DMSO- d_6) of **6** exhibited a multiplet near δ 6.90-7.80 due to aromatic protons. Aromatic protons(9H) of **7** were resonated at δ 6.90-7.70, while methylene protons (8H) were observed at δ 3.13-3.50 in the form of multiplet.

Further, in order to establish the versatility of 2-bromoalkylideneprapanedinitriles (**1**) as synthons, **1** reacted with 2-amino-3-carbethoxycyclopenta[4,5]thiophenes (**4**) and 3-substituted 4-amino-5-carbethoxythiazole-2-thiones (**5**). When **1** reacted with **4** in propanol at $70\text{-}80^\circ\text{C}$ the intermediates (**8**) formed were easily underwent cyclization forming triheterocycles (**9**) in a single step and in no case intermediates (**8**) were isolated. Compounds (**1**) on reaction with **5** also predicted to proceed in the similar way to provide thiazolopyrrolopyrimidones (**11**), but instead in all the attempted reactions the uncyclic products 3-substituted 4-(1-substituted 2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (**10**) were recovered (Scheme 2).

The reactions between **1** and π -deficient systems having pyridine or pyrimidine nucleus (**12**) were unsuccessful under the conditions exploited for π -excessive substrates (**3**) and (**4**) and in all the cases starting compounds (**12**) were recovered (Scheme 3). Therefore, it could easily be concluded that the formation of triheterocycles is facilitated with a π -excessive ring such as benzene, thiophene etc., while it is hindered in π -deficient rings such as pyridine and pyrimidine.



Scheme 2



Scheme 3

IR(KBr) spectra of **9** showed absorptions near 3120 and 3050-2840 cm^{-1} for N-H and C-H along with the characteristic C=C, C=N stretching vibrations at 1604-1492 cm^{-1} . The sharp bands near 2210 and 1670 cm^{-1} were assigned to cyano and carbonyl functionalities respectively. ^1H NMR(DMSO- d_6) of **9** exhibited multiple bands due to methylene protons(6H) in the region δ 3.15-3.70, while a multiplet due to aromatic protons was obtained at δ 6.85-8.45. The NH ring proton was absorbed downfield at δ 10.30-10.50.

IR(KBr) spectra of **10** exhibited two prominent bands in the region $3450\text{--}3280\text{ cm}^{-1}$ for amino group which supported the formation of uncyclic products (**10**). A sharp absorption for cyano group was obtained near 2210 cm^{-1} together with a sharp absorption for carbonyl moiety of ester group near 1670 cm^{-1} . The signals due to C=C, C=N and C=S stretching vibrations were obtained near $1596\text{--}1488$ and $1300\text{--}1200\text{ cm}^{-1}$ respectively. Moreover the presence of triplet of $\text{CH}_3(3\text{H})$ at $\delta\ 1.20\text{--}1.40$ and quartet of $\text{CH}_2(2\text{H})$ at $\delta\ 4.10\text{--}4.40$ respectively due to ethyl protons together with a broad absorption due to amino protons (2H) near $\delta\ 5.50\text{--}5.60$. Aromatic protons were resonated at $\delta\ 7.10\text{--}7.80$ in the form of multiplet.

EXPERIMENTAL

Melting points were determined on electrothermal apparatus (capillary method) and are uncorrected. The IR spectra were performed on a Buck scientific spectrophotometer using potassium bromide technique. The TLC were performed using silica gel G and spots were exposed in iodine vapour. The ^1H NMR spectra were taken in DMSO-d_6 on Varian model 100-400 spectrometer using TMS as an internal standard. MS spectra were recorded on Jeol D-300 Mass Spectrometer.

The procedures given for the synthesis of **6,7,9** and **10** were utilized in the formation of compounds (**6a-6h**, **7**, **9a-9d** and **10a-10c**).

1,7-Disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (6a-6h) (General procedure)

To the well stirred solution of 2-bromo-1-arylalkylidenepropanedinitriles¹ (**2**) (0.011 mol) in propanol (40 mL) was added the solution of 5-substituted 2-aminobenzophenones (**3**) (0.01 mol) in propanol (20 mL) in portions at 65°C during the period of 30 min. After the addition was completed the reaction mixture was further stirred for 5-6 h at the same temperature and for 2 h at rt. The cold reaction mixture was poured on to the crushed ice (150 g), the solid separated was filtered, washed with aqueous ethanol (20 % v/v) followed by water, dried and crystallized from a mixture of ethanol : DMF (4 : 6) to yield the following pyrrolo[1,2-*a*]quinazolines (**6**).

1,5-Diphenyl-2-cyanopyrrolo[1,2-*a*]quinazoline (6a). yield : 41 %; mp : $287\text{--}289^\circ\text{C}$; UV (methylene chloride) : 375(4.18), 283(4.51); IR(KBr) : $2220(\text{CN})\text{ cm}^{-1}$; ^1H NMR(DMSO- d_6) : $\delta\ 6.90\text{--}7.80$ (m, 15H, Ar-H); MS : 345(M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{15}\text{N}_3$: C, 83.45; H, 4.38; N, 12.17. Found : C, 83.78; H, 4.59; N, 12.37.

1-(4-Methylphenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6b). yield : 41 %; mp : $281\text{--}283^\circ\text{C}$; UV (methylene chloride) : 373(4.22), 283(4.43); IR(KBr) : $2210(\text{CN})\text{ cm}^{-1}$; ^1H NMR(DMSO- d_6) : $\delta\ 2.45$ (s, 3H, CH_3), $7.10\text{--}8.00$ (m, 14H, Ar-H); MS : 359(M^+). Anal. Calcd for $\text{C}_{25}\text{H}_{17}\text{N}_3$: C, 83.54; H, 4.77; N, 11.69. Found : C, 83.78; H, 4.54; N, 11.89.

1-(4-Methoxyphenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6c). yield : 40 %; mp : 247-249 °C; UV(methylene chloride) : 374(4.18), 280(4.49); IR(KBr) : 2210(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 3.17(s, 3H, OCH₃), 7.25-8.17(m, 14H, Ar-H); MS : 375(M⁺). Anal. Calcd for C₂₅H₁₇N₃O : C, 79.78; H, 4.57; N, 11.19. Found : C, 78.59; H, 4.48; N, 11.32.

1-(4-Chlorophenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6d). yield : 48 %; mp : 277-279 °C; UV(methylene chloride) : 282(4.47), 247(4.49); IR(KBr) : 2220(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 7.20-8.10 (m, 14H, Ar-H); MS : 382(M+2). Anal. Calcd for C₂₄H₁₄N₃Cl : C, 75.84; H, 3.71; N, 11.06. Found : C, 75.58; H, 3.61; N, 11.36.

1,5-Diphenyl-2-cyano-7-chloropyrrolo[1,2-*a*]quinazoline (6e). yield : 43 %; mp : 308-310 °C; UV(methylene chloride) : 282(4.47), 247(4.49); IR(KBr) : 2220(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 7.00-8.10 (m, 14H, Ar-H); MS : 382(M+2). Anal. Calcd for C₂₄H₁₄N₃Cl : C, 75.84; H, 3.71; N, 11.06. Found : C, 75.58; H, 3.61; N, 11.36.

1-(4-Methylphenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6f). yield : 42 %; mp : 285-287 °C; UV(methylene chloride) : 292(4.47), 246(4.45); IR(KBr) : 2210(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 2.55(s, 3H, CH₃); 7.00-8.10 (m, 13H, Ar-H); MS : 396(M+2). Anal. Calcd for C₂₅H₁₆N₃Cl : C, 76.23; H, 4.10; N, 10.67. Found : C, 76.03; H, 4.39; N, 10.41.

1-(4-Methoxyphenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6g). yield : 40 %; mp : 302-304 °C; UV(methylene chloride) : 273(4.15), 268(4.16); IR(KBr) : 2210(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 3.85(s, 3H, OCH₃); 7.00-8.10 (m, 13H, Ar-H); MS : 412(M+2). Anal. Calcd for C₂₅H₁₆N₃OCl : C, 73.26; H, 3.94; N, 10.25. Found : C, 73.54; H, 4.21; N, 10.59.

1-(4-Chlorophenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6h). yield : 51 %; mp : 321-323 °C; UV(methylene chloride) : 283(4.51), 253(4.52); IR(KBr) : 2210(CN) cm^{-1} ; $^1\text{H NMR(DMSO-}d_6)$: δ 3.85(s, 3H, OCH₃); 7.10-8.10 (m, 13H, Ar-H); MS : 416(M+2). Anal. Calcd for C₂₄H₁₃N₃Cl₂ : C, 69.58; H, 3.17; N, 10.14. Found : C, 69.76; H, 3.39; N, 10.01.

3-Chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (7).

To the well stirred solution of 2-chlorohexalidenepropanedinitriles¹ (**2**) (1.853 g, 0.011 mol) in propanol(40 mL) was added the solution of 2-amino-5-chlorobenzophenone (**3**) (2.315 g, 0.01 mol) in propanol(20 mL) in portions at 65 °C over a period of 30 min. After the addition was completed, the reaction mixture was further stirred for 6 h at the same temperature and for 2 h at rt. The cold reaction mixture was poured on to the crushed ice(150 g), the solid separated was filtered, washed with aqueous ethanol(20 % v/v) followed by water, dried and crystallized from a mixture of ethanol : DMF(6:3) to obtain 40 % yield of **7**. mp : 310-312 °C; UV(methylene chloride) : 394(3.98), 246(4.48); IR(KBr) : 3080-2850(CH),

2220(CN) cm^{-1} ; $^1\text{H NMR}(\text{DMSO-}d_6)$: δ 3.15-3.50(m, 8H, $(\text{CH}_2)_4$); 6.90-7.70 (m, 12H, Ar-H); MS : 360(M+2). Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_3\text{Cl}$: C, 73.84; H, 4.51; N, 11.74. Found : C, 73.61; H, 4.81; N, 11.99.

1-Substituted 2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-ones (9) (General procedure)

The solution of 2-bromo-1-arylalkylidenepropanedinitriles (**1**) (0.01 mol) in propanol(40 mL) was added the solution of 2-amino-3-carbethoxycyclopenta[4,5]thiophenes¹¹ (**4**) in propanol(20 mL) at 65-70 °C. After the addition was completed the reaction mixture was stirred at 70-80 °C temperature for 6-7 h and for 1 h at rt. The cold reaction mixture was poured on to the crushed ice, solid obtained was filtered, washed with aqueous ethanol(20 % v/v) followed by water, dried and crystallized from DMF:ethanol(6 : 4) mixture.

1-Phenyl-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9a). yield : 40%; mp : 285-287 °C; IR(KBr) : 3120(NH), 2990-2850(CH), 2210(CN), 1676(CO) cm^{-1} ; $^1\text{H NMR}(\text{DMSO-}d_6)$: δ 3.15-3.70(m, 6H, $(\text{CH}_2)_3$); 6.85-8.10 (m, 12H, Ar-H); 10.50 (s, 1H, NH); MS : 331(M⁺). Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{N}_3\text{OS}$: C, 68.86; H, 3.93; N, 12.68. Found : C, 69.02; H, 4.20; N, 12.89.

1-(4-Methylphenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9b). yield : 40%; mp : >360 °C; IR(KBr) : 3124(NH), 3010-2860(CH), 2220(CN), 1670(CO) cm^{-1} ; $^1\text{H NMR}(\text{DMSO-}d_6)$: δ 2.60(s, 3H, CH_3); 3.15-3.70 (m, 6H, $(\text{CH}_2)_3$); 7.15-8.40 (m, 12H, Ar-H); 10.30 (s, 1H, NH); MS : 345(M⁺). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{OS}$: C, 69.54; H, 4.27; N, 12.16. Found : C, 69.90; H, 4.45; N, 11.96.

1-(4-Methoxyphenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9c). yield : 45%; mp : 336-338 °C; IR(KBr) : 3120(NH), 3010-2860(CH), 2210(CN), 1672(CO) cm^{-1} ; $^1\text{H NMR}(\text{DMSO-}d_6)$: δ 3.20-3.65 (m, 6H, $(\text{CH}_2)_3$); 3.90 (s, 3H, OCH_3); 7.20-8.45(m, 12H, Ar-H); 10.30 (s, 1H, NH); MS : 361(M⁺). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: C, 66.46; H, 4.18; N, 11.62. Found : C, 66.66; H, 4.29; N, 11.51.

1-(4-Chlorophenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9d). yield : 48%; mp : 313-315 °C; IR(KBr) : 3128(NH), 2990-2850(CH), 2210(CN), 1672(CO) cm^{-1} ; $^1\text{H NMR}(\text{DMSO-}d_6)$: δ 3.15-3.70(m, 6H, $(\text{CH}_2)_3$); 6.90-7.70 (m, 12H, Ar-H); 10.60 (s, 1H, NH); MS : 368(M+2). Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{N}_3\text{OClS}$: C, 62.38; H, 3.31; N, 11.49. Found : C, 62.58; H, 3.73; N, 11.71.

3-Substituted 4-(2-amino-3-cyano-4-substituted pyrrol-1-yl)-5-carbethoxythiazole-2-thiones (10) (General procedure) To the well stirred solution of 2-bromo-1-arylalkylidenepropanedinitriles (**1**) (0.01 mol) in DMF (50 mL) heated at 65 °C was added powdered 3-substituted 4-amino-5-carbethoxythiazole-2-thiones¹² (**5**) (0.01 mol) portionwise and the reaction mixture was stirred at 75-80 °C for 6-8 h and for 1 h at rt. The solution obtained was added to crushed ice(150 g), solid separated was filtered, washed with water followed by ethanol(20 % v/v), dried and crystallized from a mixture of DMF : ethanol (4:6).

3-Phenyl-4-(2-amino-3-cyano-4-phenylpyrrol-1-yl)-5-carbethoxythiazole-2-thione (10a). yield : 40%; mp : 295-297 °C; IR(KBr) : 3430, 3320(NH), 2220(CN), 1670(CO), 1290, 1200(CS) cm^{-1} ; ^1H NMR(DMSO- d_6) : δ 1.20-1.40 (t, $J = 6.2$ Hz, 3H, CH_2CH_3); 4.10-4.30(q, $J = 6.2$ Hz, 2H, CH_2CH_3); 5.50-5.60 (s, 2H, NH_2); 7.30-7.80 (m, 13H, Ar-H); MS : 446(M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_2$: C, 61.86; H, 4.06; N, 12.55. Found : C, 61.49; H, 4.16; N, 12.69.

3-Phenyl-4-[2-amino-3-cyano-4-(methoxyphenyl)pyrrol-1-yl]-5-carbethoxythiazole-2-thione (10b). yield : 33%; mp : 269-271 °C; IR(KBr) : 3420, 3290(NH), 2220(CN), 1680(CO), 1300, 1200(CS) cm^{-1} ; ^1H NMR(DMSO- d_6) : δ 1.20-1.35(t, $J = 6.0$ Hz, 3H, CH_2CH_3); 3.90-4.00 (s, 3H, OCH_3); 4.20-4.40 (q, $J = 6.0$ Hz, 2H, CH_2CH_3); 5.50-5.60 (s, 2H, NH_2); 7.10-7.70 (m, 12H, Ar-H); MS : 476(M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_3\text{S}_2$: C, 60.48; H, 4.23; N, 11.76. Found : C, 60.21; H, 4.01; N, 11.39.

3-(4-Chlorophenyl)-4-(2-amino-3-cyano-4-phenylpyrrol-1-yl)-5-carbethoxythiazole-2-thione (10c). yield : 40%; mp : 268-270 °C; IR(KBr) : 3400, 3280(NH), 2205(CN), 1670(CO), 1300, 1210(CS) cm^{-1} ; ^1H NMR(DMSO- d_6) : δ 1.20-1.40 (t, $J = 6.3$ Hz, 3H, CH_2CH_3); 4.10-4.30(q, $J = 6.3$ Hz, 2H, CH_2CH_3); 5.50-5.55(s, 2H, NH_2); 7.30-7.85(m, 12H, Ar-H); MS : 483($\text{M}+2$). Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_4\text{O}_2\text{ClS}_2$: C, 57.43; H, 3.56; N, 11.65. Found : C, 57.05; H, 3.81; N, 11.44.

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