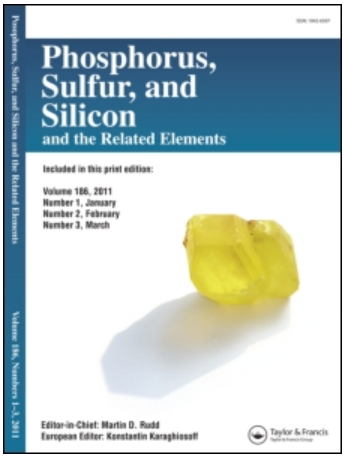

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Cyanothioacetanilide Intermediates in Heterocyclic Synthesis, Part 1: Synthesis and Biological Evaluation of Some Novel Thiazole, Thiophene, Pyrazole, and Pyrazolo[1,5-a]Pyrimidine Derivatives

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CYANOTHIOACETANILIDE INTERMEDIATES IN HETEROCYCLIC SYNTHESIS, PART 1: SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL THIAZOLE, THIOPHENE, PYRAZOLE, AND PYRAZOLO[1,5-a]PYRIMIDINE DERIVATIVES

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Some novel thiophenes (4a,b, 5, and 9a,b) were obtained from the cycloalkylation of the thiocarbamoyl group in the cyanothioacetanilide derivative (1) with α-halocarbonyl compounds. Also, the reaction of cyanothioacetanilide derivative with phenyl isothiocyanate in the presence of potassium hydroxide followed by in situ heterocyclization of the resulting adduct with α-halocarbonyl compounds furnished the corresponding thiazole (12, 14, and 15), pyrazole (19), and pyraozlo[1,5-a]pyrimidine (22, 25, and 26) derivatives. Compounds (4b, 5, 9a, 12, 13, 18, 22, 25, and 26) were tested to evaluate their antimicrobial activity.

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Keywords Biological activity; cyanothioacetanilide; pyrazolo[1,5-a]pyrimidines; thiazoles; thiophenes

INTRODUCTION

Cyanothioacetanilide derivatives are highly reactive reagents, and their utility in heterocyclic synthesis has recently received considerable attention.[1–3] The combination of NH-C═S and CH_2CN groups in cyanothioacetanilide molecules opens a variety of synthetic opportunities for further reaction and utilization as a starting materials in the synthesis of heterocyclic compounds. The development of effective therapeutic agents for the treatment of inflammation continues to be challenging problem in medicinal chemistry. Compounds containing thiophene, thiazole, and pyrazole functionalities have been reported to exhibit anti-inflammation activities.[4–9] In our laboratory, a series of thiazole and pyrazole derivatives has been synthesized and evaluated in the search for new non-steroidal anti-inflammation.[10–16] Furthermore, the antimicrobial activity of thiophene, thiazole, and pyrazole are well documented.[17,18] The present investigation deals with the synthesis of

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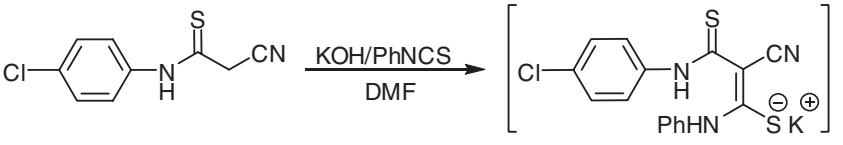
compounds having thiophene, thiazole, and pyrazole incorporated in their structures in order to investigate their effect on antimicrobial activity.

RESULTS AND DISCUSSION

Cyanothioacetanilide (**1**) has three nucleophilic sites, which may potentially undergo initial attack; the methylene group carbon and thioamide nitrogen and sulfur atoms. On the whole, under cyclocondensation or cycloaddition, cyanothioacetanilide acts a C,N-, C,S-, or S,N-binucleophile. Also, the cyanothioacetanilide contains a cyano group as electrophile center. In the course of our study of synthetic scope of cyanothioacetanilide (**1**), we investigated its reaction with different reagents as well as the structure and transformation of the reaction product.

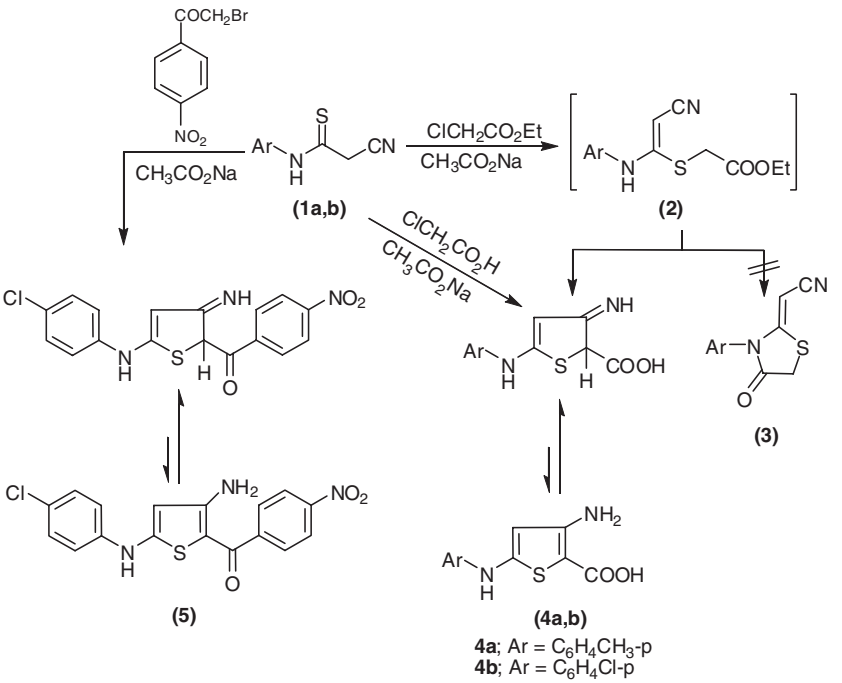
α-Halocarbonyl compounds are highly versatile intermediates for the synthesis of a variety of heterocyclic compounds.[19] Treatment of cyanothioacetanilides (**1a**,**b**) with ethyl chloroacetate in alcoholic sodium acetate under reflux afforded a single product in each case. The structure of the isolated products was established by analytical and spectroscopic data as the thiophene derivatives (**4a**,**b**) instead of the thiazole derivative (**3**). The infrared spectrum of compound **4a** showed the absence of a C≡N group, which supports the thiophene structure and the presence of the following absorption bands: 3294–3000 (br; OH/NH), 2920 (CH-aliph.), and 1707cm^{-1}(C=O; COOH). Also, the ^{1}H NMR spectrum of compound **4a** in DMSO-d_6 displayed three singlets at 2.23, 3.68, and 5.78 ppm attributed to CH_3 and 2H of thiophene protons, respectively. The aromatic protons were observed as a multiplet at 7.08–7.46; also three singlets were identified at 9.73, 10.07, and 11.48 ppm attributed to 2NH and OH carboxylic group (disappeared with D_2O). This suggested that the reaction starts with a nucleophilic substitution of the chlorine atom by the thiolate group of (**1**) to give the non-isolable intermediate **2**, which cyclizes through the addition on the cyano group. Also, the reaction involves the hydrolysis of an ester group under the reaction conditions. The structure of the latter compound **4a**,**b** was further confirmed by another route via alkylation of compound **1** with chloroacetic acid under the same conditions (Scheme 1). In a similar manner, thiophene derivative **5** was obtained by the cycloalkylation of cyanothioacetanilide derivative (**1b**) with *p*-nitrophenacyl bromide. The structure of **5** was identified on the basis of satisfactory elemental analysis and spectral data. The infrared spectrum showed the absence of the C≡N functional group and indicated the presence of absorption bands at 3102 (NH) and 1660 cm^{-1} (C=O). The mass spectrum of **5** showed a molecular ion peak at *m/z* = 373 (7%), which is characteristic for the molecular formula $C_{17}H_{12}ClN_3O_3S$ together with base peak at *m/z* 219.

The reactivity of the methylene group in cyanothioacetanilide derivative (**1**) towards isothiocyanate in the presence of potassium hydroxide followed by in situ heterocyclization with α-halocarbonyl compounds was studied. Thus, the reaction of cyanothioacetanilide derivative (**1b**) with phenyl isothiocyanate in the presence of potassium hydroxide at room temperature gave the non-isolable potassium salt (**6**).

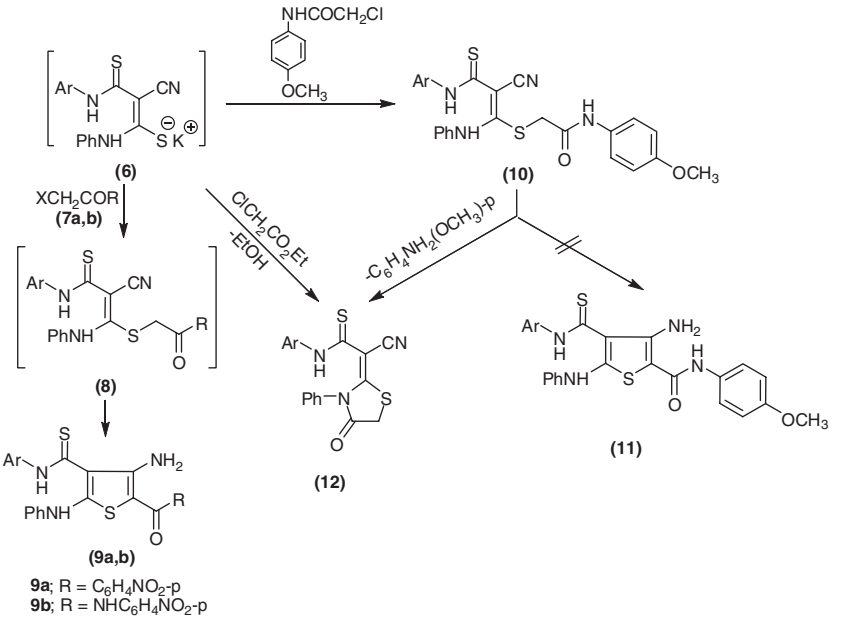


(1b) **(6)**

The potassium sulfide salt (**6**) was exploited to synthesize new thiophene and thiazole derivatives. Treatment of the intermediate **6** with p-nitrophenacyl bromide (**7a**) and *N*-(4-nitrophenyl)chloroacetamide (**7b**) at room temperature gave the novel 3-aminothiophene derivatives (**9a**,**b**) in good yields (Scheme 2). The structure of the isolated products was confirmed on the basis of elemental analysis and spectral data. The infrared spectrum of **9a** revealed absorption bands at 3393, 3320, 3280 (NH/NH_2) and 1660 cm^{-1} (C=O) with the absence of a C≡N absorption band. Also, the ^1H NMR spectrum of **9a** in DMSO-d_6 exhibited a broad singlet at 8.01 (2H, NH_2) and a D_2O exchangeable 2NH at 9.94, 10.11 ppm. Also, compound **9b** gave a molecular ion peak at *m/z* 507 [M-16(NH_2); 20%] and the base peak was found in the spectrum at *m/z* 343. The formation of **9** is assumed to proceed through the initial alkylation of intermediate **6** to afford the non-isolable thioether derivative (**8**) followed by in situ heterocyclization via a Dieckmann-type reaction.[20,21] On the other hand, the isolable thioether derivative (**10**) was obtained via alkylation of salt (**6**) with *N*-(4-methoxyphenyl)-chloroacetamide in good yield. The structure of thioether (**10**) was confirmed by examining spectral data. Its infrared spectrum indicated the presence of NH, C≡N, and C=O absorption bands. In addition the structure **10** was supported by ^1H NMR spectrum, which revealed a singlet at $\delta = 3.67$ ppm assigned to the methylene moiety. 4-Thiazolidinone derivative (**12**) was obtained via refluxing of thioether derivative (**10**) in ethanolic piperidine, and the other possible thiophene structure (**11**) was excluded on the basis of analytical and spectral data. Infrared spectrum exhibited absorption bands at 2199 (C≡N) and 1737 cm^{-1} (C=O; thiazolidinone), while its ^1H NMR spectrum showed a singlet at δ 4.00 (2H, CH_2-thiazole). The reaction mechanism is assumed to proceed via intramolecular cyclization and elimination of *p*-anisidine molecule. The structure of the



Scheme 1

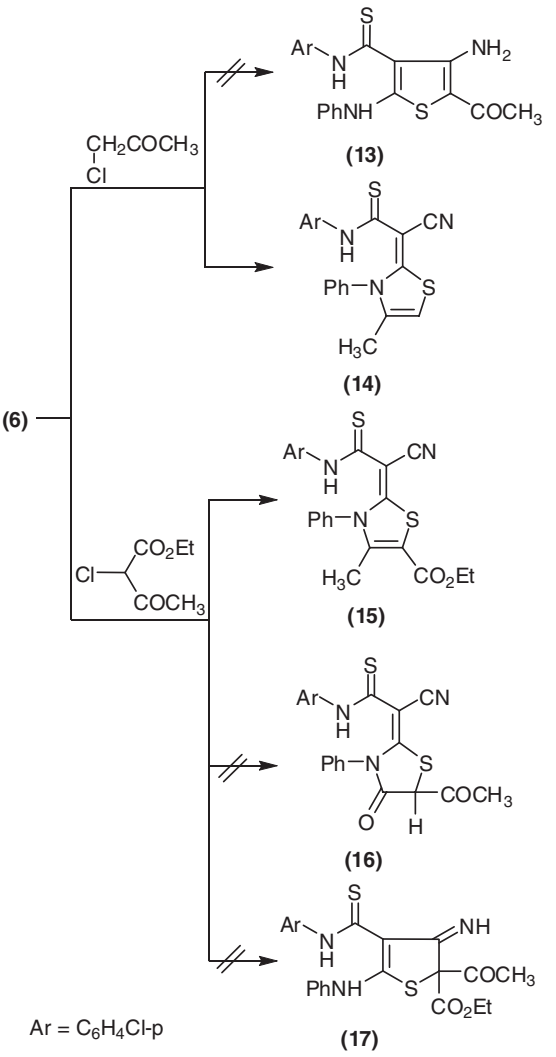


Scheme 2

latter compound was further confirmed by synthetic route via cycloalkylation of salt (**6**) with ethyl chloroacetate.

Cycloalkylation of non-isolable salt (**6**) with chloroacetone afforded 4-methylthiazole derivative (**14**). The other possible structure (**13**) was ruled out on the basis of infrared spectrum, which showed the characteristic absorption band at 2182 cm^{-1} for C≡N functional group and ^1H NMR spectrum, which revealed a singlet at $\delta = 1.84$ ppm assigned to CH_3 with singlet at δ 6.37 ppm assigned to (CH-thiazole). Similarly, treatment of non-isolable salt (**6**) with α-chloroethylacetoacetate afforded 4-methylthiazle derivative (**15**), and the two other possible structures (**16** and **17**) were excluded on the basis of elemental analysis and spectral data. The infrared spectrum of compound **15** showed the characteristic absorption band at 2184 and 1712 cm^{-1} for C≡N and (C=O, ester) groups. Also, ^1H NMR revealed a triplet at 1.31 ppm and quartet at 4.32 ppm assigned to the ester moiety. Formation of **15** was assumed to proceed through initial alkylation followed by intramolecular cyclization through dehydration (Scheme 3).

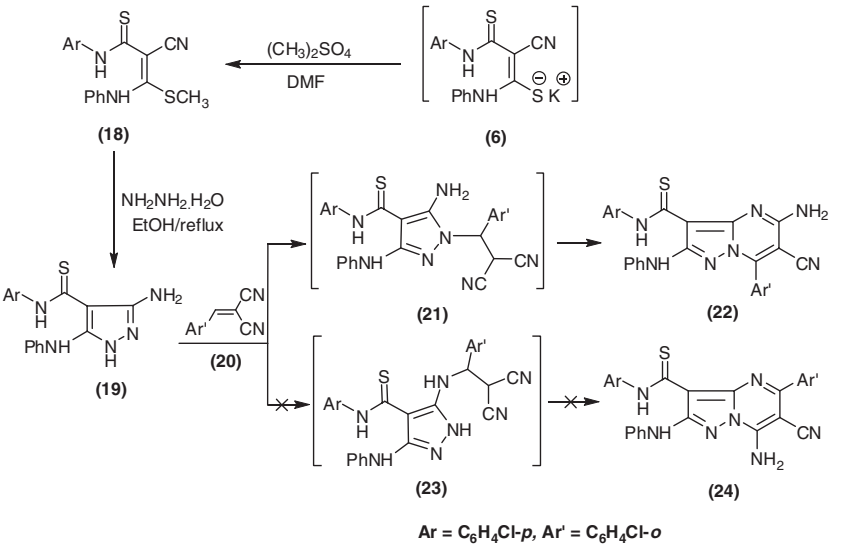
Pyrazole derivatives have attracted the attention of organic chemists due to their biological and chemotherapeutic importance.[22] Also, the pyrazolo[1,5-a]pyrimidine structural motif may be found in a large number of pharmacological agents with a diverse range of physiological activities, for example the treatment of pain, including inflammatory and neuropathic pain.[23] The study was extended to synthesize some novel pyrazolo[1,5-a]pyrimidines from readily obtainable inexpensive starting materials. The key starting material for this part of the research was obtained when the non-isolable **6** was treated with dimethyl sulfate. The isolated product was identified as *N*-(4-chlorophenyl)-2-cyano-3-(methylthio)-3-(phenylamino)prop-2-enethioamide (**18**) on the basis of: (a) the infrared spectrum showed absorption bands at 3134 (NH), 2950 (CH-aliph.) and 2198 cm^{-1} (C≡N), (b) ^1H NMR spectrum in DMSO-d_6 displayed three singlets at 2.26 assigned for methyl



Scheme 3

sulfanyl group, (c) it is converted into the aminopyrazole (**19**) by refluxing with hydrazine in ethanol (Scheme 4). The infrared spectrum of compound **19** showed the absence of characteristic absorption bands for C≡N, with the presence of absorption bands at 3252, 3111 cm^{-1} (NH/NH_2). ^1H NMR spectrum of compound **19** revealed the following signals: δ 6.15 (s, 2H, NH_2) and D_2O exchangeable 3 NH at 9.15, 9.80, and 10.00 ppm. Also, compound **19** gave a molecular ion peak at *m/z* 343, which fitted exactly with the expected molecular weight. The reactivity of aminopyrazole derivative **19** towards some electrophilic reagents was investigated to afford pyrazolo[1,5-a]pyrimidine derivatives. Thus, reaction of **19** with α-cyano-2-chlorocinnamonitrile (**20**) yielded a product for which structure **22** or **24** seemed possible. Structure **22** appears more likely than **24** on the basis that ring nitrogen is the most nucleophilic center in the molecule.[24] The structure of **22** was established by elemental analysis and spectral data. Infrared spectrum of compound **22** showed the

following absorption bands: 3305, 3252, 3179 (NH/NH_2) and 2219 cm^{-1} (C≡N). ^1H NMR spectrum of compound **22** in DMSO-d_6 revealed D_2O exchangeable signals at 9.25, 9.38, and 9.95 ppm for NH_2 and 2NH. The formation of **22** is assumed to proceed via initial Michael addition of endocyclic NH of **19** to the activated double bond of **20** to afford the intermediate **21** followed by intramolecular cyclization and auto-oxidation Scheme 4.



Scheme 4

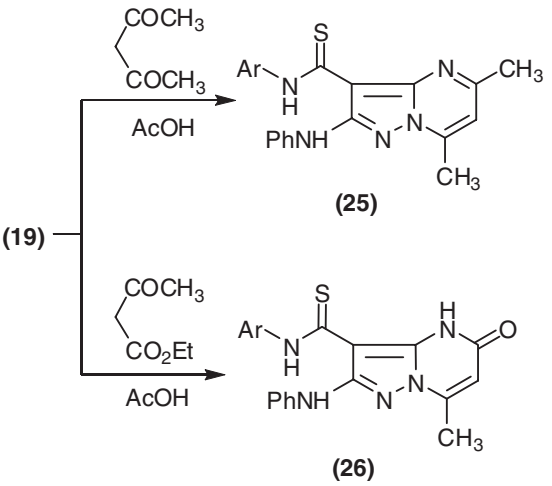
Also, the reactivity of the aminopyrazole derivative (**19**) towards the 1,3-dicarbonyl compounds was also discussed. Thus, cyclocondensation of aminopyrazole (**19**) with acetylacetone in refluxing glacial acetic acid gave the pyrazolo[1,5-a]pyrimidine derivative (**25**). Finally the reaction of **19** with ethyl acetoacetate in refluxing glacial acetic yielded pyrazolo[1,5-a]pyrimidine derivative (**26**) (Scheme 5).

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (v, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC MS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University.

General Procedure for the Formation of Compounds (4a,b)

Method A. A mixture of cyanothioacetanilide derivatives **1a**,**b**[25] (0.01 mol), ethyl chloroacetate (0.01 mol), and fused sodium acetate (0.01 mol) was refluxed in ethanol (30 mL) for 1 h. The solid product, which precipitated upon heating, was collected and recrystallized from the proper solvent to give **4a**,**b**.



Scheme 5

Method B. A mixture of cyanothioacetanilide derivatives **1a**,**b** (0.01 mol), chloroacetic acid (0.01 mol), and fused sodium acetate (0.01 mol) was refluxed in ethanol (30 mL) for 1 h. The solid product, which was produced upon heating, was collected and recrystallized from the proper solvent to give **4a**,**b**.

3-Imino-5-(p-tolylamino)-2,3-dihydrothiophene-2-carboxylic acid 4a. This compound was crystallized from dioxane and obtained in 60% yield as white crystals, mp 240–242°C, IR (KBr): $\nu = 3294$–3000 (br; OH/2NH), 2920 (CH-aliph.) and 1707 cm^{-1} (C=O, COOH); ^1H NMR (DMSO-d_6): $\delta = 2.23$, (s, 3H, CH_3), 3.68, 5.78 (2s, 2H, thiophene-H), 7.08–7.46 (m, 4H, Ar-H), 9.73, 10.07, 11.48 ppm (3s, 3H, 2NH + OH; disappeared with D_2O). Anal. Calcd. for $C_{12}H_{12}N_2O_2S$ (248): C, 58.06; H, 4.83; H, 11.29. Found: C, 58.00; H, 4.70; H, 11.20.

3-Imino-5-(p-chlorophenylamino)-2,3-dihydrothiophene-2-carboxylic acid 4b. This compound was crystallized from acetic acid and obtained in 65% yield as white crystals, mp 270–272°C, IR (KBr): $\nu = 3300$–3000 (br; OH carboxylic, 2NH) and 1708 cm^{-1} (C=O, COOH); ^1H NMR (DMSO-d_6): $\delta = 3.92$, 5.85 (2s, 2H, thiophene-H), 7.27–7.67 (2d, 4H, Ar-H), 10.04 (s, 1H, NH; disappeared with D_2O), 11.20 (br, 2H, NH + OH; disappeared with D_2O). Anal. Calcd. for $C_{11}H_9ClN_2O_2S$ (268.5): C, 49.16; H, 3.35; H, 10.42. Found: C, 49.10; H, 3.30; H, 10.30.

N-(4-Chlorophenyl)-4-imino-5-(4-nitrobenzoyl)-4,5-dihydrothiophen-2-amine (5)

A mixture of cyanothioacetanilide **1b** (0.01 mol), *p*-nitrophena-cyl bromide (0.01 mol), and fused sodium acetate (0.01 mol) was refluxed in ethanol (30 mL) for 1 h. The solid product, which was produced upon heating, was collected and recrystallized from acetic acid to give **5**.

Yield (50%), mp 220–222°C, IR (KBr): $\nu = 3102\ cm^{-1}$ (NH) and $1660\ cm^{-1}$ (C=O); MS, m/z (%): 373 (7), 219 (100, base peak), 355 (7), 221 (9) and 150 (37). Anal. Calcd.

for $C_{17}H_{12}ClN_3O_3S$ (373.5): C, 54.61; H, 3.21; N, 11.24. Found: C, 54.50; H, 3.10; N, 11.20.

Preparation of 9a,b, 10, 12, 13, and 15: General Procedure

To a suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethylformamide (15 mL), cyanothioacetanilide derivative **1b** (0.01 mol) and then the phenyl isothiocyanate (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature with α-halocarbonyl compound (0.01 mol) and left at room temperature for 3 h. Then it was poured into ice/water and acidified with 0.1 *N* HCl at pH 3–4. The resulting precipitate was filtered off, dried, and recrystallized from the proper solvent.

Alternative Method for Preparation of Compound 12

A mixture of compound **10** (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h. The solid product, which was produced upon heating, was collected and recrystallized to give **12**.

4-Amino-N-(4-chlorophenyl)-5-(4-nitrobenzoyl)-2-(phenylamino)-thiophene-3-carbothioamide (9a). This compound was crystallized from benzene and obtained in 70% yield as brown crystals, mp >300°C, IR (KBr): ν = 3393, 3280 cm^{-1} (NH_2/NH) and 1660 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ = 7.11–8.29 (m, 13H, Ar-H), 8.01 (br, 2H, NH_2, disappeared with D_2O), 9.94, 10.11 (2s, 2H, 2NH, disappeared with D_2O). Anal. Calcd. for $C_{24}H_{17}ClN_4O_3S_2$ (508.5): *C*, 56.63; H, 3.34; N, 11.01. Found: *C*, 56.50; H, 3.20; N, 11.00

3-Amino-4-(4-chlorophenylcarbamothioyl)-N-(4-nitro-phenyl)-5-(phenylamino)thiophene-2-carboxamide (9b). This compound was crystallized from benzene and obtained in 65% yield as brown crystals, mp >300°C, IR (KBr): ν = 3306 (br, NH_2/NH) 3063 (CH-aromatic) and 1650 cm^{-1} (C=O; amide). Anal. Calcd. for $C_{24}H_{18}ClN_5O_3S_2$ (523.5): *C*, 55.01; H, 3.43; N, 13.37. Found: *C*, 55.00; H, 3.30; N, 13.20. MS, *m/z* (%) = 507 [M-16 (NH_2) 20], 343 (100, base peak), 508 (67.7), 216 (52.7) and 127 (71).

2-(3-(4-Chlorophenylamino)-2-cyano-1-(phenylamino)-3-thioxo-prop-1-enylthio)-N-(4-methoxyphenyl)acetamide (10). This compound was obtained in 75% yield as white crystals (acetic acid), mp 200–202°C. IR (KBr): ν = 3259 (NH), 2200 (C≡N) and 1639 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ = 3.67 (s, 3H, OCH_3), 3.73 (s, 2H, SCH_2), 6.75–7.54 (m, 13H, Ar-H), 9.74, 10.08, 11.20 (3s, 3H, 3NH, disappeared with D_2O). Anal. Calcd. for $C_{25}H_{21}ClN_4O_2S_2$ (508.5): *C*, 58.99; H, 4.12; N, 11.01. Found: C, 58.80; H, 4.00; N, 10.70.

***N*-(4-Chlorophenyl)-2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-ethanethioamide (12).** This compound was obtained in 55% yield as yellow crystals (benzene), mp 240–242°C. IR (KBr): ν = 3330 (NH), 2198 (C≡N) and 1737 cm^{-1} (C=O; thiazolidinone). ^1H NMR (DMSO-d_6): δ = 4.00 (s, 2H, SCH_2), = 7.32–7.58 (m, 9H, Ar-H), 9.58 (s, 1H, NH; disappeared with D_2O). Anal. Calcd. for $C_{18}H_{12}ClN_3OS_2$ (385.5): C, 56.03; H, 3.11; N, 10.89. Found: C, 55.90; H, 3.00; N, 10.80.

N-(4-Chlorophenyl)-2-cyano-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene)-ethanethioamide (13). This compound was obtained in 55% yield as yellow crystals (benzene), mp 237–240°C. IR (KBr): ν = 3305 (NH), 2182 (C≡N) and 1304 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): δ = 1.84 (s, 3H, CH_3), 6.94 (s, 1H, thiazole-H), 7.25–7.59 (m, 9H,

Ar-H), 8.87 (s, 1H, NH; disappeared with D_2O). Anal. Calcd. for $C_{19}H_{14}ClN_3S_2$ (383.5): C, 59.45; H, 3.65; N, 10.95. Found: C, 59.30; H, 3.60; N, 10.80.

Ethyl 2-(2-(4-Chlorophenylamino)-1-cyano-2-thioxoethylidene)-4-methyl-3-phenyl-2,3-dihydrothiazole-5-carboxylate (15). This compound was obtained in 60% yield as brown crystals (benzene), mp 245–247°C. IR (KBr): $\nu = 3409$ (NH), 2184 (C≡N) and 1712 (C=O; ester), 1301 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): $\delta = 1.31$ (t, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 7.29–7.62 (m, 9H, Ar-H), 9.11 (s, 1H, NH; disappeared with D_2O). Anal. Calcd. for $C_{22}H_{18}ClN_3O_2S_2$ (455.5): C, 57.95; H, 3.95; N, 9.22. Found: C, 57.80; H, 3.80; N, 9.30.

N-(4-Chlorophenyl)-2-cyano-3-(methylthio)-3-(phenylamino)prop-2-enethioamide (18)

To a stirred suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethylformamide (15 mL) at room temperature, the active methylene **1b** (0.01 mol) and next phenyl isothiocyanate (0.01 mol) were added gradually. The reaction mixture was stirred at room temperature for 3 h, then treated with dimethylsulfate (0.01 mol) and stirred at room temperature for an additional 3 h. Then it was poured into ice/water, the resulting product was filtered off, dried, and recrystallized from EtOH as white crystals.

Yield 80%, mp 140–143°C. IR (KBr): $\nu = 3334$ (NH), 2950 (CH-aliph.) and 2198 (C≡N), 1359 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): $\delta = 2.26$ (s, 3H, CH_3), 6.52–7.61 (m, 9H, Ar-H), 9.76, 11.67 (2s, 2H, 2NH; disappeared with D_2O). Anal. Calcd. for $C_{17}H_{14}ClN_3S_2$ (359.5): C, 56.74; H, 3.89; N, 11.68. Found: C, 56.70; H, 3.90; N, 11.50.

3-Amino-*N*-(4-chlorophenyl)-5-(phenylamino)-*1H*-pyrazole-4-carbothioamide (19)

A mixture of **18** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was heated under reflux for 3 h. The reaction was concentrated, and the obtained product was collected and recrystallized from benzene as yellow crystals.

Yield 70%, mp 180–182°C. IR (KBr): $\nu = 3252$, 3111 (NH_2/NH), 3065 (CH-arom.) and 1620 cm^{-1} (C=N) 1350 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): $\delta = 5.35$ (s, 2H, NH_2; disappeared with D_2O), 6.46–7.68 (m, 9H, Ar-H), 9.15 (s, 1H, NH; disappeared with D_2O), 9.80 (br, 2H, 2NH, disappeared with D_2O). Anal. Calcd. for $C_{16}H_{14}ClN_5S$ (343.5): C, 55.89; H, 4.07; N, 20.37. Found: C, 55.80; H, 4.00; N, 20.00.

5-Amino-7-(2-chlorophenyl)-N-(4-chlorophenyl)-6-cyano-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbothioamide (22)

To a solution of **19** (0.01 mol) in ethanol (30 mL), α-cyano-2-chlorophenylcinnamonitrile **20** (0.01 mol) and piperidine (0.5 mL) were added, and the mixture was heated under reflux for 3 h. The solid product was collected and recrystallized from dioxane as brown crystals.

Yield 50%, mp 220–222°C. IR (KBr): $\nu = 3305$, 3252, 3179 (NH_2/NH) and 2219 (C≡N), 1340 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): $\delta = 7.01$–7.93 (m, 13H, Ar-H), 9.25 (s, 2H, NH_2, disappeared with D_2O), 9.38, 9.95 (2s, 2H, 2NH, disappeared with D_2O). Anal. Calcd. for $C_{26}H_{17}Cl_2N_7S$ (530): C, 58.86; H, 3.20; N, 18.49. Found: C, 58.70; H, 3.20; N, 18.40.

Preparation of Compounds 25 and 26: General Procedure

A mixture of compound **19** (0.01 mol) and 1,3-dicarbonyl compounds (namely, acetylacetone, ethyl acetoacetate, 0.01 mol) in glacial acetic acid (10 mL) was heated under reflux for 1 h. The solid product, which was produced upon heating, was collected and recrystallized from the proper solvent to give **25** and **26**.

***N*-(4-Chlorophenyl)-5,7-dimethyl-2-(phenylamino)pyrazolo[1,5-a]pyramidine-3-carbothioamide (25).** This compound was obtained in 75% yield as brown crystals (dioxane), mp 225–227°C. IR (KBr): ν = 3289 (NH), 2934 (CH-aliph.) and 1620 (C=N), 1295 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): δ = 2.50, 2.64 (2s, 6H, $2CH_3$), 5.92 (s, 1H, pyrimidine-H), 7.02–7.86 (m, 9H, Ar-H), 8.90, 10.04 (2s, 2H, 2NH; disappeared with D_2O). Anal. Calcd. for $C_{21}H_{18}ClN_5S$ (407.5): C, 61.84; H, 4.41; N, 17.17. Found: C, 61.70; H, 4.30; N, 17.10.

***N*-(4-Chlorophenyl)-7-methyl-5-oxo-2-(phenylamino)-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3-carbothioamide (26).** This compound was obtained in 65% yield as brown crystals (DMF), mp >300°C. IR (KBr): ν = 3290 (NH), 2927 (CH-aliph.) and 1657 cm^{-1} (C=O), 1295 cm^{-1} (C=S). Anal. Calcd. for $C_{20}H_{16}ClN_5OS$ (409.5): C, 58.60; H, 3.90; N, 17.09. Found: C, 58.50; H, 3.80; N, 16.90. MS, *m/z* (%) = 409 (2.5%) 265 (100, base peak), 391 (35), 374 (10), 264 (34).

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