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Reactions with heterocyclic amidines: Synthesis of several new pyrazolo[1,5-a]pyrimidines and pyrazolo[1,5-a][1,3,5]triazines

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ABSTRACT

N-Bis(methylthio)methylenecyanamide (1) was allowed to react with ethylcyanoacetate or malononitrile in the presence of potassium carbonate in dimethylsulfoxide to yield the urea derivatives (3a,b), which on treatment with hydrazine hydrater resulted the corresponding aminopyrazole derivatives (4a,b). The cyclic amidine 5-amino-3-ureido-1*H*-pyrazole-4-carboxylic acid ethyl ester (4a) is found to be useful intermediate for the synthesis of new pyrazolopyrimidine and pyrazolotriazine derivatives (5-22a,b). The chemical structures of the synthesized compounds (3a,b-22a,b) were characterized by their elemental analyses, FT-IR, ^{1}H ^{13}C NMR and mass spectra.

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1. Introduction

Aminopyrazoles are versatile intermediates for the synthesis of biologically interesting pyrazole derivatives. Various types of biological activity have been established for pyrazolopyrimidines and pyrazolotriazines. Pyrazolo[1,5-*a*] pyrimidines [1,2] are purine analogues and have useful properties as purine antimetabolites [3] in biochemical reactions. Compounds of this class have attracted a wide pharmaceutical interest because of their antitrypanosomal [4,5], antischistosomal activity [6], antibacterial [7,8], anti-viral [9,10], as CRF1 antagonist [11], HMG-COA reductase inhibitors [12], COX-2 selective inhibitors [13], AMP phosphor-diesterase inhibitors [14] and as KDR kinase inhibitors [15].

N-Bis(methylthio)methylenecyanamide (**1**), [16,17] is an extremely interesting electrophilic reagent for the introduction of not only an aminomethylene group of amines and active methylene compounds but also a C=N-C=N unit in the synthesis of heterocyclic compounds [18,19]. The aim of this study was to investigate the action of several electrophilic reagents on 5-amino-3-ureido-1*H*-pyrazole-4-carboxylic acid ethyl ester (**4a**) in the synthesis of new pyrazolopyrimidine and pyrazolotriazine derivatives.

2. Experimental

2.1. Instrumentation

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra (KBr) were recorded on a Beckman Acculab 1. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC-250 spectrometer, the calibration of spectra were carried out by means of solvents peaks ($CDCl_3$: δ ^{1}H 7.25 ppm, δ ^{13}C 77.00 ppm; $(CD_3)_2SO$: δ ^{1}H 2.52 ppm, ^{13}C 40.45 ppm). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.00 ppm). Mass spectra were recorded on a spectrometer (electron impact) Varian CH-5. Elemental analysis was carried out at Microanalysis Unit at Cairo University.

2.2. Synthesis

2.2.1. General procedure for the reaction of N-bis (methyl thio)methylenecyananamide (1) with ethyl cyanoacetate and malononitrile

A mixture of *N-bis*(methylthio)methylenecyananamide (**1**) (1.46 g, 0.01 mole) and ethyl cyanoacetate or malononitrile (0.015 mole) in (20 mL) of dimethylsulfoxide in presence of

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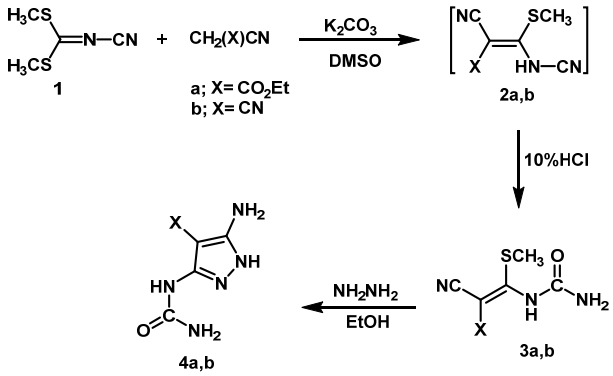


Scheme 1

potassium carbonate (2.7 g, 0.02 mole) was stirred at room temperature for 4 h.

The reaction mixture was poured portion wise into 50 mL of 10% hydrochloric acid containing crushed ice. The obtained precipitate was collected by filtration and crystallized from appropriate solvent to yield compound **3a** and **3b**, respectively (Scheme 1).

2-Cyano-3-methylsulfanyl-3-ureido-acrylic acid ethyl ester (**3a**): Color: Colourless needles. Yield: 85%. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3414 (NH_2), 3283 (NH), 2214 (CN), 1700, 1689 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.23-1.37 (t, 3H, CH_3), 2.54 (s, 3H, S-Me), 4.10-4.18 (q, 2H, -CH_2), 7.07 (br.s, 2H, NH_2), 10.21 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.27 (1C, SCH_3), 16.26 (1C, CH_3), 60.98 (1C, CH_2), 67.21 (1C, =C-CN), 116.76 (1C, CN), 152.20 (1C, $CONH_2$), 163.68 (1C, COOET), 169.35 (1C, =C-SMe). MS (EI, *m/z* (%)): 229 (M^+, 31). Anal. calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33; S, 13.99. Found: C, 42.45; H, 4.88; N, 17.98; S, 13.75%.

(2,2-Dicyano-1-methylsulfanyl-vinyl)-urea (**3b**): Color: Buff crystals. Yield: 83%. M.p.: 295-297 °C. FT-IR (KBr, ν, cm^{-1}): 3341-3446 (NH_2), 3223 (NH), 2203-2214 (2CN), 1673 (C=O)(amide). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 2.5 (s, 3H, SMe), 7.6-7.93 (br.s, 2H, NH_2), 10.95 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 12.61 (1C, SCH_3), 115.12 (1C, =C-CN), 143.42 (1C, CN), 153.07 (1C, CN), 158.55 (1C, $CONH_2$), 176.49 (1C, =C-SMe). MS (EI, *m/z* (%)): 182 (M^+, 43). Anal. calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75; S, 17.60. Found: C, 39.73; H, 3.61; N, 30.43; S, 17.34%.

2.2.2. General procedure for the reaction of 3a and 3b with hydrazine hydrate

A mixture of compound **3a** or **3b** (0.01 mole), hydrazine hydrate (1 mL) in 20 mL ethanol was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the solid formed was crystallized from appropriate solvent to yield compound **4a** and **4b**, respectively (Scheme 1).

5-Amino-3-ureido-1H-pyrazole-4-carboxylic acid ethyl ester (**4a**): Color: Colourless needles. Yield: 61%. M.p.: 246-248 °C. FT-IR (KBr, ν, cm^{-1}): 3358-3491 (2NH_2), 3212 (NH), 1691-1647 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.21-1.27 (t, 3H, CH_3), 4.15-4.23 (q, 2H, -CH_2), 6.12 (br.s, 2H, -NH_2), 7.1 (br.s, 2H, NH_2), 7.67 (s, 1H, NH), 11.34 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.29 (1C, CH_3), 14.60 (1C, =C-NH_2), 38.69 (1C, N=C-NH), 59.25 (1C, CH_2), 60.95 (1C, =C-COOEt, 154.59 (1C, $CONH_2$), 163.98 (1C, COOEt). MS (EI, *m/z* (%)): 213 (M^+, 66). Anal. calcd. for $C_7H_{11}N_5O_3$: C, 39.44; H, 5.20; N, 32.85. Found; C, 39.41; H, 4.95; N, 32.78%.

(5-Amino-4-cyano-1H-pyrazol-3-yl)-urea (**4b**): Color: Buff crystals. Yield: 48%. M.p.: 262-264 °C. FT-IR (KBr, ν, cm^{-1}): 3357-3479 (2NH_2), 3280 (NH), 2185 (CN), 1693 (C=O) (amide). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 6.18 (br.s, 2H, NH_2), 6.4 (br.s, 2H, NH_2), 11.5 (s, 1H, NH), 12.15 (s, 1H, NH). MS (EI, *m/z* (%)): 166 (M^+, 33). Anal. calcd. for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 36.41; H, 3.47; N, 50.43%.

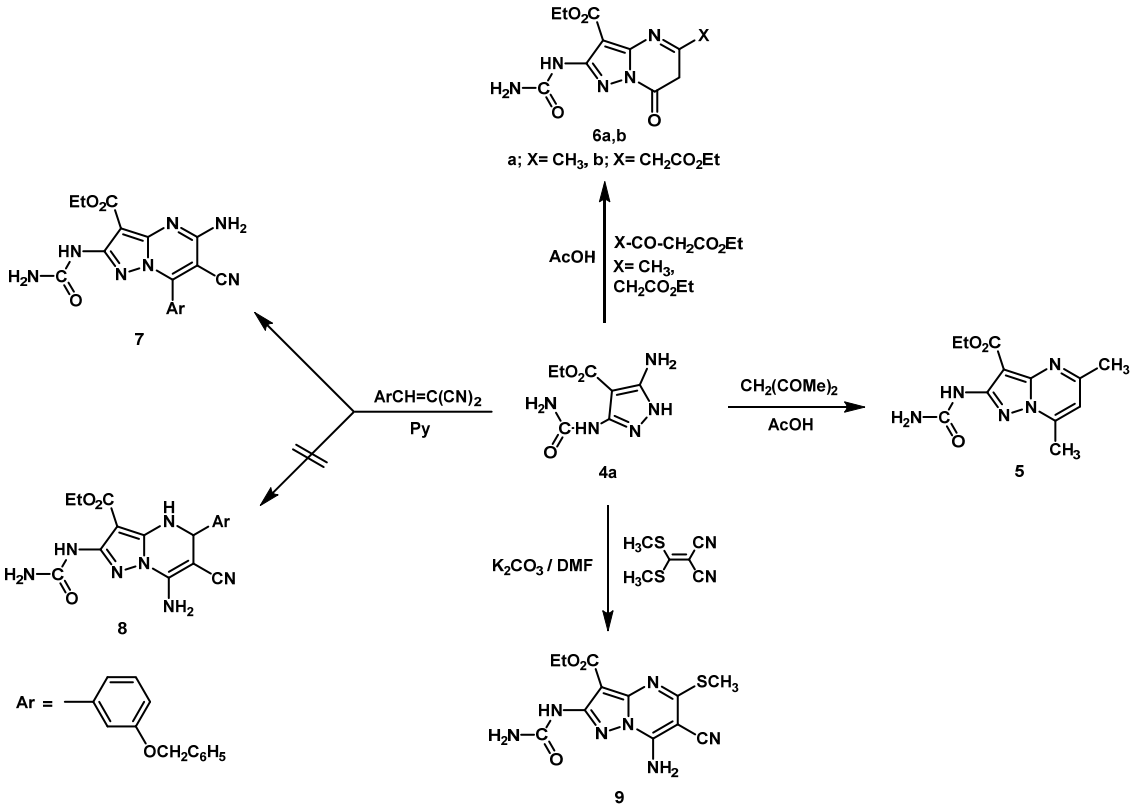
2.2.3. General procedure for the synthesis of pyrazolo[1,5-a] pyrimidines 5 and 6a,b

To a solution of compound **4a** (2.13 g, 0.01 mole) in (10 mL) acetic acid, (0.01 mole) of acetylacetone, ethylaceto acetate or diethyl-3-oxo-gluturate) was added. The reaction mixture was refluxed for the appropriate time (7-14 h). After cooling the reaction mixture was poured into water. The solid product formed crystallized from appropriate solvent to yield compound **5**, **6a** and **6b**, respectively (Scheme 2).

5,7-Dimethyl-2-ureido-pyrazolo[1, 5-a]pyrimidine-3-carboxy lic acid ethyl ester (**5**): Color: Buff crystals. Yield: 56%. M.p.: 289-270 °C. FT-IR (KBr, ν, cm^{-1}): 3369-3478 (NH_2), 3229 (NH), 1693, 1660 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.18 (q, 2H, CH_2), 6.0-6.2 (s, 3H, NH_2 + Ar-H), 6.2 (8.72 (s, 1H, NH). MS (EI, *m/z* (%)): 277 (M^+, 35). Anal. calcd. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.92; H, 5.46; N, 25.46%.

5-Methyl-7-oxo-2-ureido-6, 7-dihydro-pyrazolo[1,5-a]pyrimi dine-3-carboxylic acid ethyl ester (**6a**): Color: Buff crystals. Yield: 65%. M.p.: 267-269 °C. FT-IR (KBr, ν, cm^{-1}): 3304-3477 (NH_2), 3294 (NH), 1693, 1640 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.28-1.32 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.24-4.33 (q, 2H, CH_2), 5.88 (s, 2H, CH_2), 5.95 (s, 2H, NH_2), 11.23 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.70 (1C, CH_3), 19.06 (1C, CH_3), 59.65 (1C, CH_2), 83.56 (1C, CH_2CO), 99.65 (1C, =C-CH_3), 143 (1C, =C-N), 144 (1C, N=C-N), 149 (1C, =C-COOEt), 154 (1C, $CONH_2$), 157 (1C, COOEt), 162.89 (1C, C=O). MS (EI, *m/z* (%)): 279 (M^+, 27). Anal. calcd. for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found; C, 46.98; H, 4.35; N, 24.78%.

5-Ethoxycarbonylmethyl-7-oxo-2-ureido-6, 7-dihydro-pyra zolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (**6b**): Color: Buff crystals. Yield: 46%. M.p.: 255-257 °C. FT-IR (KBr, ν, cm^{-1}): 3319-3447 (NH_2), 3274 (NH), 1715, 1701, 1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15 (t, 3H, CH_3), 1.22 (t, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.14-4.23 (q, 2H, -CH_2), 4.25-4.33 (q, 2H, CH_2), 5.95 (s, 2H, CH_2), 7.45 (br.s, 2H, NH_2), 11.85 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.24 (1C, CH_3), 14.59 (1C, CH_3), 60.77 (1C, CH_2), 61.26 (1C, CH_2), 84.76 (1C, N=C-), 103 (1C, CH_2 CO), 104 (1C, CH_2CO), 143.44 (1C, =C-N), 147.25 (1C, N-C=N), 150.66 (1C, =C-COOEt), 153.74 (1C, $CONH_2$),



Scheme 2

154.42 (1C, COOEt), 162.19 (1C, COOEt), 168.79 (1C, C=O). MS (EI, *m/z* (%)): 351 (M^+, 24). Anal. calcd. for $C_{14}H_{17}N_5O_6$: C, 47.86; H, 4.88; N, 19.93. Found: C, 47.87; H, 4.96; N, 19.50%.

2.2.4. Synthesis of 5-amino-7-(3-benzyloxy-phenyl)-6-cyano-2-ureido-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (7)

A solution of compound **4a** (2.13 g, 0.01 mole) and 2-(3-benzyloxybenzyliden)malononitrile (2.6 g, 0.01 mole) in pyridine (20 mL) was heated under reflux for 2 h. The solvent was then evaporated in vacuum, and the remaining solid product was crystallized from methanol (Scheme 2). Color: Yellow crystals. Yield: 56%. M.p.: 222-224 °C. FT-IR (KBr, ν, cm^{-1}): 3357-3479 ($2NH_2$), 3280 (NH), 2195 (CN), 1693 (C=O). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.25-1.33 (t, 3H, CH_3), 4.14-4.23 (q, 2H, -CH_2), 5.20 (s, 2H, CH_2), 6.18 (br.s, 2H, NH_2), 6.4 (br.s, 2H, NH_2), 6.95-7.33 (m, 9H, Ar-H), 7.15 (s, 1H, NH). MS (EI, *m/z* (%)): 471 (M^+, 0.93). Anal. calcd. for $C_{24}H_{21}N_7O_4$: C, 61.14; H, 4.49; N, 20.80. Found: C, 61.34; H, 4.86; N, 20.55%.

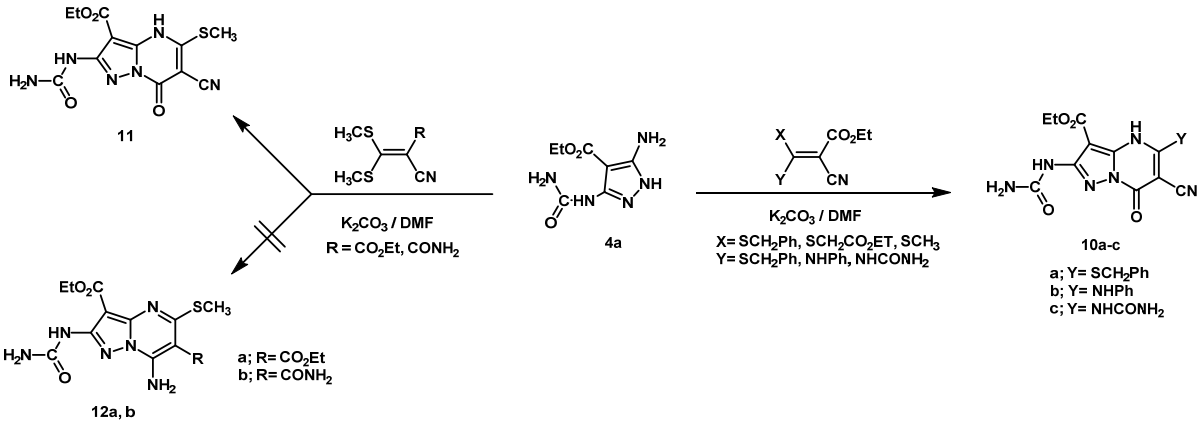
2.2.5. General procedure for the synthesis of pyrazolo[1,5-a]pyrimidines 9, 10a-c and 11

To a solution of compound **4a** (2.13 g, 0.01 mole) in (10 mL) dimethylformamide and 0.5 g potassium carbonate, an electrophilic reagent namely, 2-cyano-3,3-*bis*(methylthio) acrylonitrile, 3,3-*bis*-benzyl-sulfanyl-2-cyano-acrylic acid ethyl ester, 2-cyano-3-ethoxy-carbonylmethylsulfanyl-3-phenyl-amino acrylic acid ethyl ester, 2-cyano-3-methylsulfanyl-3-ureido-acrylic acid ethyl ester and ethyl-2-cyano-3,3-*bis*-(methylthio) acrylate and 2-cyano-3,3-*bis*-methylsulfanyl-acryl amide (0.01 mole) was added. The reaction mixture was stirred at room temperature for the appropriate time (6-14 h). After this time the reaction mixture was acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration and crystallized from appropriate solvent to yield compound **9**, **10a-c** and **11**, respectively (Scheme 3).

7-Amino-6-cyano-5-methylsulfanyl-2-ureido-pyrazolo[1, 5-a]pyrimidine-3-carboxylic acid ethyl ester (**9**): Color: Yellow crystals. Yield: 62%. M.p.: > 360 °C. FT-IR (KBr, ν, cm^{-1}): 3291-3412 ($2NH_2$), 3180 (NH), 2215 (CN), 1719-1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.23-1.37 (t, 3H, CH_3), 2.71 (s, 3H, SCH_3), 4.20-4.27 (q, 2H, -CH_2), 7.43 (br.s, 2H, NH_2), 8.74 (br.s, 2H, NH_2), 8.62 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.39 (1C, CH_3), 16.32 (1C, SCH_3), 59.74 (1C, CH_2), 84.23 (1C, =C-N), 84.5 (1C, N=C-N), 114.12 (1C, =C-NH_2), 142.94 (1C, =C-S), 153.15 (1C, =C-COOEt), 153.99 (1C, =C-CN), 154.46 (1C, CN), 157.40 (1C, $CONH_2$), 163.62 (1C, COOEt). MS (EI, *m/z* (%)): 335 (M^+, 9.6). Anal. calcd. for $C_{12}H_{13}N_7O_3S$: C, 42.98; H, 3.91; N, 29.24. Found; C, 42.84; H, 3.92; N, 29.57%.

5-Benzylsulfanyl-6-cyano-7-oxo-2-ureido-4, 7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (**10a**): Color: Buff crystals. Yield: 62%. M.p.: 322-324 °C. FT-IR (KBr, ν, cm^{-1}): 3438-3349 (NH_2), 3214 (NH), 2235 (CN), 1686, 1652, 1633 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.23 (t, 3H, CH_3), 3.77 (s, 1H, pyrimidine-NH), 4.25 (s, 2H, CH_2), 4.45-4.38 (q, 2H, CH_2), 6.65 (s, 2H, NH_2) 7.35-7.75 (m, 5H, Ar-H), 8.78 (s, 1H, NH). MS (EI, *m/z* (%)): 412 (M^+, 26). Anal. calcd. for $C_{18}H_{16}N_6O_4S$: C, 52.42; H, 3.91; N, 20.38. Found: C, 52.45; H, 4.10; N, 20.46%.

6-Cyano-7-oxo-5-phenylamino-2-ureido-4, 7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (**10b**): Color: Yellow crystals. Yield: 51%. M.p.: 343-345 °C. FT-IR (KBr, ν, cm^{-1}): 3465-3340 (NH_2), 3114-3285 (NH), 2205 (CN), 1725, 1655 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.32-1.22 (t, 3H, CH_3), 3.8 (s, 1H, pyrimidine-NH), 4.66 (s, 1H, NH-Ph), 4.42-4.15 (q, 2H, CH_2), 5.63 (s, 2H, NH_2), 8.53 (s, 1H, NH), 7.05-



Scheme 3

7.45 (m, 5H, Ar-H). MS (EI, *m/z* (%)): 381 (M^+, 11). Anal. calcd. for $C_{17}H_{15}N_7O_4$: C, 53.54; H, 3.96; N, 25.71. Found: C, 53.65; H, 4.15; N, 25.55%.

6-Cyano-7-oxo-2,5-diureido-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (**10c**): Color: Colourless crystals. Yield: 60%. M.p.: 341-343 °C. FT-IR (KBr, ν, cm^{-1}): 3413-3211 (NH_2 and NH), 2221 (CN), 1684, 1652 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.25-1.15 (t, 3H, CH_3), 3.90 (s, 1H, pyrimidine-NH), 4.35-4.18 (q, 2H, CH_2), 5.8 (s, 2H, NH_2), 6.55-6.65 (br.s, 2H, NH_2), 8.49 (s, 1H, NH), 8.85 (s, 1H, NH). MS (EI, *m/z* (%)): 348 (M^+, 10). Anal. calcd. for $C_{12}H_{12}N_8O_5$: C, 41.38; H, 3.47; N, 32.17. Found: C, 41.65; H, 3.78; N, 32.45%.

6-Cyano-5-methylsulfanyl-7-oxo-2-ureido-4, 7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (**11**): Color: Colourless crystals. Yield: 69%. M.p.: 358-360 °C. FT-IR (KBr, ν, cm^{-1}): 3374-3495 ($2NH_2$), 3158 (NH), 2230 (CN), 1705, 1662 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 2.50-2.47 (t, 3H, CH_3), 2.45 (s, 3H, SMe), 3.88 (s, 1H, pyrimidine-NH), 4.26-4.35 (q, 2H, -CH_2), 7.17 (br.s, 2H, NH_2), 8.32 (s, 1H, NH). MS (EI, *m/z* (%)): 336 (M^+, 13). Anal. calcd. for $C_{12}H_{12}N_6O_4S$: C, 42.85; H, 3.60; N, 24.99. Found: C, 42.56; H, 3.66; N, 25.28%.

2.2.6. General procedure for the reactions of compound 4a with ethoxymethylenemalononitrile and ethoxymethylene cyanoacetate

To a solution of compound **4a** (2.13 g, 0.01 mole) in (10 mL) acetic acid, ethoxymethylene malononitrile or ethoxy methylene cyanoacetate (0.01 mole) was added. The reaction mixture was refluxed for the appropriate time (4-6 h). After this time the reaction mixture was poured into water. The solid product formed crystallized from appropriate solvent to yield compound **13a** and **13b**, respectively (Scheme 4).

5-Amino-6-cyano-2-ureido-pyrazolo[1, 5-a]pyrimidine-3-carboxylic acid ethyl ester (**13a**): Color: Yellow crystals. Yield: 47%. M.p.: 357-359 °C. FT-IR (KBr, ν, cm^{-1}): 3413-3213 (NH_2 and NH), 2213 (CN), 1700, 1689 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.32 (t, 3H, CH_3), 4.2-4.35 (q, 2H, -CH_2), 7.10 (br.s, 2H, NH_2), 7.88 (br.s, 2H, NH_2), 8.50 (s, 1H, Ar-H), 9.15 (br.s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 19.7 (1C, CH_3), 65.7 (1C, CH_2), 83.00 (1C, =C-N), 93.36 (1C, N=C-N), 120.9 (1C, N=C-NH_2), 153.4 (1C, C=C-N) , 154.3 (1C, =C-COOEt), 158.7 (1C, =C-CN), 159.5 (1C, CN), 161.5 (1C, $CONH_2$), 169.5 (1C, COOEt). MS (EI, *m/z* (%)): 289 (M^+, 5). Anal. calcd. for $C_{11}H_{11}N_7O_3$: C, 45.68; H, 3.83; N, 33.90. Found: C, 45.96; H, 3.63; N, 33.91%.

5-Amino-2-ureido-pyrazolo[1, 5-a]pyrimidine-3,6-dicarboxylic acid diethyl ester (**13b**): Color: Yellow crystals. Yield: 51%. M.p.: 337-339 °C. FT-IR (KBr, ν, cm^{-1}): 3345-3456 (NH_2), 3165 (NH), 1722, 1680 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.21-1.34 (m, 6H, $2CH_3$), 4.20-4.35 (m, 4H, $2CH_2$), 6.65 (br.s, 2H, NH_2), 8.15 (br.s, 2H, NH_2), 8.40 (s, 1H, Ar'H), 9.10 (br.s, 1H, NH). MS (EI, *m/z* (%)): 336 (M^+, 22). Anal. calcd. for $C_{13}H_{16}N_6O_5$: C, 46.43; H, 4.80; N, 24.99. Found: C, 46.66; H, 4.65; N, 24.80%.

2.2.7. Synthesis of 4-amino-2-methylsulfanyl-7-ureido-pyrazolo[1,5-a][1,3,5]triazine-8-carboxylic acid ethyl ester (14)

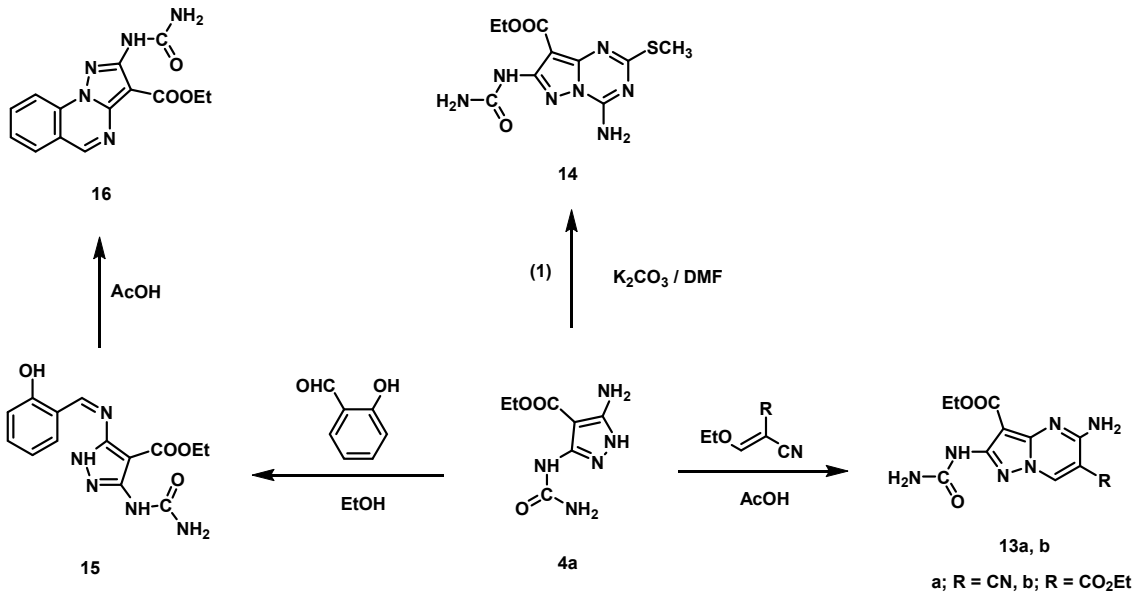
To a solution of compound **4a** (2.13 g, 0.01 mole) in (10 mL) dimethylformamide and 0.5 g potassium carbonate, *N-bis*(methylthio)methylenecyanamide (**1**) (1.46 g, 0.01 mole) was added. The reaction mixture was stirred at room temperature for 6bh. After this time the reaction mixture was acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration and crystallized from dimethylformamide (Scheme 4). Color: Yellow crystals. Yield: 66%. M.p.: 357-358 °C. FT-IR (KBr, ν, cm^{-1}): 3325-3436 (NH_2), 3277 (NH), 1722, 1684 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.32 (t, 3H, CH_3), 2.40 (s, 2H, NH_2), 2.46 (s, 3H, SMe), 4.20-4.30 (q, 2H, -CH_2), 7.25 (s, 2H, NH_2), 8.7 (s, 1H, NH). MS (EI, *m/z* (%)): 311 (M^+, 32). Anal. calcd. for $C_{10}H_{13}N_7O_3S$: C, 38.58; H, 4.21; N, 31.49. Found: C, 38.86; H, 4.53; N, 31.61%.

2.2.8. Synthesis of 5-[(2-Hydroxy-benzylidene)amino]-3-ureido-1H-pyrazolo-4-carboxylic acid ethyl ester (15)

To a solution of compound **4a** (2.13 g, 0.01 mole) in (10 mL) ethanol and (0.1 mL) piperidine, 2-hydroxybenzaldehyde (1.2 g, 0.01 mole) was added. The reaction mixture was refluxed for 2 h, and the obtained product was crystallized from chloroform (Scheme 4). Color: Yellow crystals. Yield: 78%. M.p.: 279-380 °C. FT-IR (KBr, ν, cm^{-1}): 3345-3456 (NH_2 and OH), 3165 (NH), 1722, 1682 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.35 (t, 3H, CH_3), 3.67 (s, 1H, pyrazole-NH), 4.20-4.30 (q, 2H, -CH_2), 6.65 (s, 2H, NH_2), 7.35-8.25 (m, 4H, Ar-H), 8.2 (s, 1H, CH-benzylideneimin), 10.65 (s, 1H, NH), 12.7 (br.s, 1H, OH). MS (EI, *m/z* (%)): 317 (M^+, 100). Anal. calcd. for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.76; N, 22.07. Found: C, 52.85; H, 4.65; N, 22.32%.

2.2.9. Synthesis of 2-ureido-pyrazolo[1,5-a]quinazoline-3-carboxylic acid ethyl ester (16)

To a solution of compound **15** (3.17 g, 0.01 mole) in acetic acid (20 mL) was heated under reflux for 4 h.



Scheme 4

The solvent was then evaporated under vacuo, and the remaining solid product was crystallized from dimethyl formamide (Scheme 4). Color: Red crystals. Yield: 82%. M.p.: 312-314 °C. FT-IR (KBr, ν, cm^{-1}): 3355-3656 (NH_2), 3165 (NH), 1725, 1695 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.18-1.32 (t, 3H, CH_3), 4.15-4.37 (q, 2H, CH_2), 6.95 (br.s, 2H, NH_2), 7.45-8.15 (m, 4H, Ar'H), 8.30 (s, 1H, NH), 9.20 (s, 1H, CH-quinazoline). MS (EI, *m/z* (%)): 299 (M$^+$, 18). Anal. calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.45; H, 4.24; N, 23.72%.

2.2.10. Synthesis of diazotization of 5-amino-3-ureido-1H-pyrazole-4-carboxylic acid ethyl ester (4a)

A cold solution of sodium nitrite 1.5 g in (10 mL) of water was added dropwisely to a stirred mixture of compound **4a** (2.13 g, 0.01 mole), HCl (10 mL, 5%) and glacial acetic acid (10 mL). The mixture was stirred at 0-5 °C for 1/2 h and the resulting diazotized solution **17** was used directly in the next reactions (Scheme 5).

2.2.11. General procedure for coupling of diazotized 17 with 2-naphthol, resorcinol, malononitrile and ethylcyanoacetate

A solution of diazonium salt **17** (0.01 mole) was added to a solution of the appropriate coupling reagent namely, 2-napthol, resorcinol, ethylcyanoacetate or malononitrile (0.01 mole) in ethanol (50 mL) in the presence of sodium acetate (5g). The solid product formed on standing was collected by filtration and crystallized from the appropriate solvent to give compound **18**, **20**, **22a** and **22b**, respectively (Scheme 5).

5-(2-Hydroxy-naphthalen-1-ylazo)-3-ureido-1H-pyrazole-4-carboxylic acid ethyl ester (**18**): Color: Red crystals. Yield: 65%. M.p.: 312-314 °C. FT-IR (KBr, ν, cm^{-1}): 3445-3326 (NH_2 and OH), 3165 (NH), 1720, 1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.22-1.32 (t, 3H, CH_3), 3.62 (s, 1H, pyrazole-H), 4.15-4.27 (q, 2H, CH_2), 6.60 (s, 2H, NH_2), 7.25-8.90 (m, 6H, Ar'H), 10.80 (br.s, 1H, OH), 12.15 (s, 1H, NH). MS (EI, *m/z* (%)): 368 (M$^+$, 26). Anal. calcd. for $C_{17}H_{16}N_6O_4$: C, 55.43; H, 4.38; N, 22.82. Found: C, 55.66; H, 4.63; N, 22.71%.

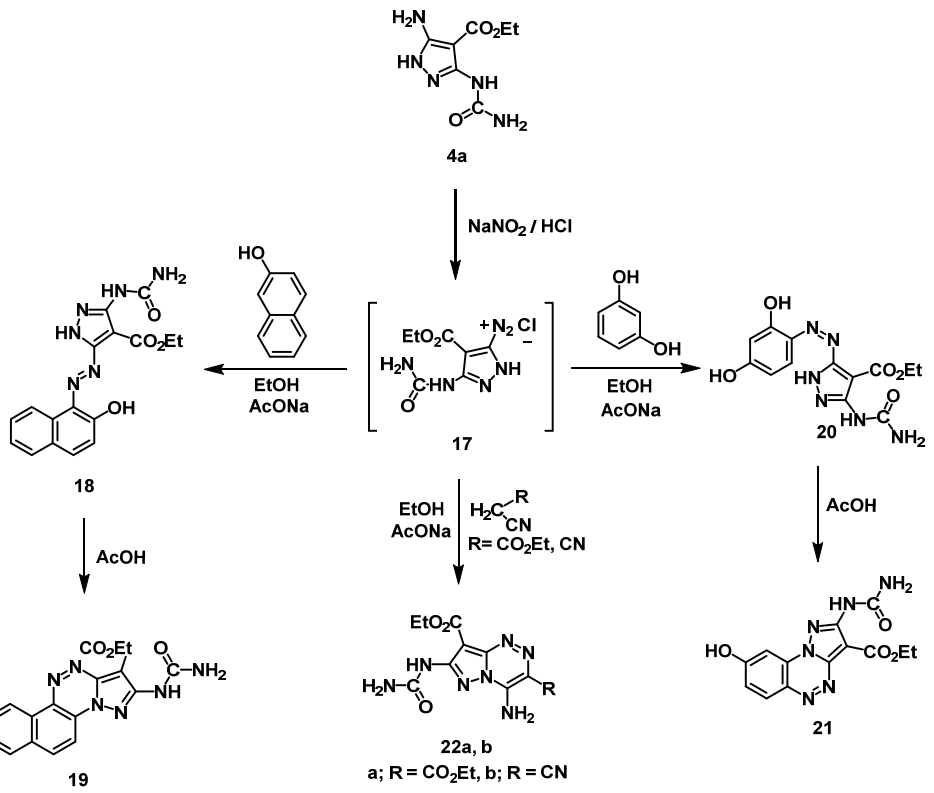
5-(2,4-Dihydroxy-phenylazo)-3-ureido-1H-pyrazole-4-carboxylic acid ethyl ester (**20**): Color: Orange crystals. Yield: 83%. M.p.: 337-339 °C. FT-IR (KBr, ν, cm^{-1}): 3445-3315 (NH_2 and OH), 3165 (NH), 1720, 1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.18-1.37 (t, 3H, CH_3), 3.69 (s, 1H, pyrazole-H), 4.16-4.28 (q, 2H, CH_2), 6.62 (br.s, 2H, NH_2), 7.26-8.12 (m, 3H, Ar-H), 11.2 (s, 1H, NH), 12.15 (br.s, 2H, 2OH). MS (EI, *m/z* (%)): 334 (M$^+$, 34). Anal. calcd. for $C_{13}H_{14}N_6O_5$: C, 46.71; H, 4.22; N, 25.14. Found: C, 46.53; H, 4.33; N, 25.43%.

4-Amino-7-ureido-pyrazolo[5,1-c][1,2,4]triazine-3,8-di carboxylic acid diethyl ester (**22a**): Color: Yellow crystals. Yield: 74%. M.p.: 341-343 °C. FT-IR (KBr, ν, cm^{-1}): 3345-3326 (NH_2), 3165 (NH), 1720, 1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.38 (m, 6H, $2CH_3$), 4.33-4.35 (m, 4H, $2CH_2$), 6.67 (s, 2H, NH_2), 7.2 (br.s, 2H, NH_2), 8.4 (s, 1H, NH). MS (EI, *m/z* (%)): 337 (M$^+$, 17). Anal. calcd. for $C_{12}H_{15}N_7O_5$: C, 42.73; H, 4.48; N, 29.07. Found: C, 42.55; H, 4.65; N, 29.25%.

4-Amino-3-cyano-7-ureido-pyrazolo[5, 1-c][1,2,4]triazine-8-carboxylic acid ethyl ester (**22b**): Color: Yellow crystals. Yield: 72%. M.p.: 310-312 °C. FT-IR (KBr, ν, cm^{-1}): 3385-3326 (NH_2), 3277 (NH), 2215 (CN), 1704, 1682 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.15-1.32 (t, 3H, CH_3), 4.20-4.35 (q, 2H, -CH_2), 6.58 (s, 2H, NH_2), 7.37 (s, 2H, NH_2), 8.38 (s, 1H, NH). MS (EI, *m/z* (%)): 290 (M$^+$, 8). Anal. calcd. for $C_{10}H_{10}N_8O_3$: C, 41.38; H, 3.47; N, 38.61. Found: C, 41.66; H, 3.54; N, 38.72%.

2.2.12. 16-ureido-11,12,14,15-tetraaza-cyclopenta[a] phenanthrene-17-carboxylic acid ethyl ester (19)

To a solution of compound **18** (3.68 g, 0.01 mol) in acetic acid (20 mL) was heated under reflux for 3 h. The solvent was then evaporated in vacuo, and the remaining solid product was crystallized from dimethylformamide (Scheme 5). Color: Red crystals. Yield: 77%. M.p.: 330-332 °C. FT-IR (KBr, ν, cm^{-1}): 3445-3326 (NH_2), 3165 (NH), 1715, 1695 (C=O's). ^{1}H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.24-1.35 (t, 3H, CH_3), 4.15-4.37 (q, 2H, CH_2), 6.95 (s, 2H, NH_2), 7.15-8.25 (m, 6H, Ar-H), 8.87 (s, 1H, NH). MS (EI, *m/z* (%)): 350 (M$^+$, 100). Anal. calcd. for $C_{17}H_{14}N_6O_3$: C, 58.28; H, 4.03; N, 23.99. Found: C, 58.45; H, 4.24; N, 23.72%.



Scheme 5

2.2.13. 8-Hydroxy-2-ureido-benzo[e]pyrazolo[5,1-c][1,2,4] triazine-3-carboxylic acid ethyl ester (21)

To a solution of compound **20** (3.34 g, 0.01 mol) in acetic acid (20 mL) was heated under reflux for 4 hrs. The solvent was then evaporated in vacuo, and the remaining solid product was crystallized from dimethylformamide (Scheme 5). Color: Yellow crystals. Yield: 85%. M.p.: 368-370 °C. FT-IR (KBr, ν, cm^{-1}): 3445-3326 (NH_2 and OH), 3165 (NH), 1715, 1695 (C=O's). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 1.17-1.31 (t, 3H, CH_3), 4.14-4.36 (q, 2H, CH_2), 6.65 (s, 2H, NH_2), 7.14-7.88 (m, 3H, Ar-H), 9.10 (s, 1H, NH), 11.45 (br.s, 1H, OH). MS (EI, *m/z* (%)): 316 (M^+, 19). Anal. calcd. for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N, 26.57. Found: C, 49.45; H, 3.64; N, 26.75%.

3. Results and discussion

3.1. Chemistry

The reaction of *N-bis*(methylthio)methylenecyanamide (**1**) with ethylcyanoacetate or malononitrile was conducted at room temperature in the presence of potassium carbonate in dimethysulfoxide followed by treatment with 10% hydrochloric acid, afforded the urea derivatives **3a**,**b**. This suggests that the isolated derivatives **3a**,**b** were formed through the intermediates **2a**,**b**. The FT-IR spectrum showed the presence of absorption bands of NH_2 and NH groups at 3414 and 3283 cm^{-1} for compound **3a**, and at 3446 and 3223 cm^{-1} for compounds **3b**, respectively. Also, the ^1H NMR spectrum showed the presence of NH_2 and NH groups at δ 7.07 and 10.21 ppm for compound **3a** and at δ 7.60 and 10.95 ppm for compound **3b**, respectively. The ^{13}C NMR of compounds **3a** and **3b** showed eight and six different signals for eight and six different carbons, respectively (Scheme 1).

The treatment of compound **3a**,**b** with hydrazine hydrate in ethanol afforded the corresponding aminopyrazole derivatives **4a**,**b** [20] (Scheme 1). The chemical structures of compounds **4a** and **4b** were in agreement with their spectral data and elemental analyses (Experimental part). The ^{13}C NMR spectrum of compound **4a** showed the presence of seven different signals corresponding to seven different carbons at δ 14.29 (1C, CH_3), 14.60 (=C-NH_2), 38.69 (N=C-NH), 59.25 (CH_2), 60.95 (=C-COOEt, 154.59 ($CONH_2$) and at δ 163.98 ppm (COOEt), which proved its structure.

Condensation of compound **4a** with acetylacetone in acetic acid yielded 5,7-dimethyl-2-ureido-pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (**5**). While the reaction of compound **4a** with ethyl acetoacetate or diethyl-3-oxoglutarate produced the corresponding pyrazolopyrimidine derivatives **6a**,**b**, respectively [21] (Scheme 2). The elemental analyses and spectroscopic data are in consistent with the assigned structures of compounds **5** and **6a**,**b**. The mass spectrum showed molecular ion peak at *m/z* 277 for compound **5**, at *m/z* 279 for compound **6a** and at *m/z* 351 for compound **6b**. ^{13}C NMR of compounds **6a** and **6b** showed eleven and fourteen different signals for eleven and fourteen different carbons, respectively (Experimental part).

Compound **4a** was reacted with 2-(3-benzyloxy-benzyliden)malononitrile in pyridine to give 5-amino-7-(3-benzyl oxy-phenyl)-6-cyano-2-ureido-4,7-dihydropyrazolo[1, 5-*a*] pyrimidine-3-carboxylic acid ethyl ester (**7**), while the other isomer **8** was not traced. The chemical Structure of compound **7** was considered more likely based on the ring nitrogen, which is the most nucleophilic centre in the molecule. Moreover, ^1H NMR showed an amino function at δ 6.7 ppm and -CH signal of C-7 at δ 5.6 ppm. The mass spectrum of compound **7** showed molecular ion peak at *m/z* 471 corresponding to its molecular formula ($C_{24}H_{21}N_7O_4$). Some

analogues related compounds reported in the literature [21-23] (Scheme 2).

Stirring an equimolar mixture of compound **4a** and 2-cyano-3,3-*bis*(methylthio)acrylonitrile [24] in dimethyl formamide containing catalytic amount of potassium carbonate at room temperature resulted in the formation of the corresponding 7-amino-6-cyano-5-methylsulfanyl-2-ureido pyrazolo [1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (**9**) (Scheme 2). The chemical structure of compound **9** was assigned on the bases of its spectral and elemental data. IR spectrum of compound **9** showed absorption bands at 3291-3412 cm^{-1} for $2NH_2$, 3180 cm^{-1} for NH, 2215 cm^{-1} for CN and at 1682-1719 cm^{-1} for 2C=O. The ^1H NMR spectrum of compound **9** showed signals at δ 1.23 for CH_3, δ 2.71 for SCH_3, δ 4.2 for CH_2, δ 7.43, 8.74 for $2NH_2$ and at δ 8.62 ppm for NH. Also, the mass spectrum showed molecular ion peak at *m/z* 335 corresponding to its formula ($C_{12}H_{13}N_7O_3S$). The ^{13}C NMR spectrum of compound **9** showed twelve different signals at δ 14.39, 16.32, 59.74, 84.23, 84.5, 114.12, 142.94, 153.15, 153.99, 154.46, 157.40, 163.62 ppm for twelve different carbon atoms, which adds additional confirmation for the proposed structure.

In a similar manner compound **4a** was reacted with 3,3-*bis*-benzyl-sulfanyl-2-cyano-acrylic acid ethyl ester [24], 2-cyano-3-ethoxy-carbonylmethylsulfanyl-3-phenyl-amino acrylic acid ethyl ester and 2-cyano-3-methylsulfanyl-3-ureido-acrylic acid ethyl ester [20], to give the corresponding pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester **10a-c**, respectively (Scheme 3). The mass spectra of compounds **10a-c** showed molecular ion peaks at *m/z* 412 for compound **10a**, at *m/z* 381 for compound **10b** and at *m/z* 348 for compound **10c**, led to the assignment of their molecular formulae.

Analogously, condensation of compound **4a** with ethyl-2-cyano-3,3-*bis*(methylthio)acrylate and 2-cyano-3,3-*bis*-methyl sulfanyl-acrylamide [25], afforded the similar product 6-cyano-5-methyl-sulfanyl-7-oxo-2-ureido-4,7-dihydropyrazolo [1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (**11**). The spectral and analytical data ruled out the alternative products **12a** and **12b** (Scheme 3), where the ^1H NMR spectrum of compound **11** showed signals at δ 2.50 for CH_3, δ 2.45 for SMe, δ 3.88 for pyrimidine-NH, δ 4.26 for CH_2, δ 7.17 for NH_2 and at δ 8.32 ppm for NH, and the mass spectrum showed molecular ion peaks at *m/z* 336.

Heating of compound **4a** with ethoxymethylene malononitrile [26] or ethoxymethylene cyanoacetate in acetic acid afforded the pyrazolo pyrimidine derivatives **13a**,**b**, respectively (Scheme 4). The chemical structures of compounds **13a** and **13b** were proved according their elemental and spectroscopic data, The ^{13}C NMR spectrum of compound **13a** showed the presence of eleven different signals corresponding to thier different carbons at δ 19.7 (CH_3), 65.7 (CH_2), 83.00 (=C-N), 93.36 (N=C-N), 120.9 (N=C-NH_2), 153.4 (C=C-N) , 154.3 (=C-COOEt), 158.7 (=C-CN), 159.5 (CN), 161.5 ($CONH_2$) and at δ 169.5 ppm (COOEt), which gives additional confirmation for the proposed structure.

When compound **4a** was stirred with *N-bis*(methylthio) methylenecyanamide (**1**) in the presence of potassium carbonate in dimethylformamide at room temperature, the corresponding 4-amino-2-methylsulfanyl-7-ureido-pyrazolo [1,5-*a*][1,3,5]triazine-8-carboxylic acid ethyl ester (**14**) was obtained. Refluxing of equimolar quantities of compound **4a** and salicylaldehyde in ethanol containing catalytic amount of piperidine gave 2-ureido pyrazolo[1,5-*a*]quinazoline-3-carboxylic acid ethyl ester (**15**). Compound **15** was cyclized into the pyrazoloquinazoline **16** by refluxing in acetic acid (Scheme 4). The structures of compounds **14**, **15** and **16** were in agreement with their spectral data and elemental analyses. The mass spectrum showed molecular ion peak at *m/z* 311 for compound **14**, at *m/z* 317 for compound **15** and at *m/z* 299 for compound **16**, which were in consistent with their corresponding formulae (Experimental part).

Treatment of compound **4a** with nitrous acid in presence of concentrated hydrochloric acid/acetic acid mixture gave the corresponding diazonium salt **17** [20], which could not be isolated in pure status but its formation was indicated via coupling with some phenols and active methylene reagents.

So, coupling of the diazonium salt **17** with 2-naphthol and resorcinol afforded the corresponding arylazo derivatives **18** and **20**, respectively. Cyclic condensation of compound **18** and **20** in refluxing acetic acid gave the corresponding **19** and **21**, respectively (Scheme 5). This result is in contrast with the reported direct formation of cyclic pyrazolo[1,5-*c*][1,2,4] triazine on coupling diazotized aminopyrazoles with naphthols [27]. The elemental analyses and spectroscopic data are in consistent with the assigned structures of compounds **18**, **19**, **20** and **21**. The ^1H NMR of compounds **18** and **20** showed presence of the phenolic (OH) at δ 10.8 ppm and δ 11.2 ppm as broad peaks, respectively, which it disappeared in compound **19**. Mass spectra of compounds **18**, **19**, **20** and **21** showed ion peaks at *m/z* 368, 350, 334 and at *m/z* 316, respectively, which were in agreement with assigned structures.

In contrast to the previous results, the salt **17** was coupled with ethyl cyanoacetate to yield compound **22a** of the molecular formula $C_{10}H_{10}N_8O_3$ (*m/z* 290), which was formulated as the pyrazolo[1,5-*c*][1,3,5]triazine based on its spectral data. Thus, the FT-IR spectrum showed the presence of an amino function at 3320 cm^{-1}, and an ester carbonyl at 1720 cm^{-1}. The ^1H NMR spectrum showed an absorption band at δ 8.8 ppm that it was integrated for two protons and was assigned for the amino group. The downfield shift of this amino function could be explained by the anisotropic effect of the ring nitrogen. In addition, ^1H NMR showed two ethyl ester groups. In the same way, compound **17** was coupled with malononitrile to afford the corresponding pyrazolo[1,5-*c*] [1,3,5]triazine, **22b** (Scheme 5). The FT-IR spectrum of compound **22b** showed the presence of an amino function at 3385-3326 cm^{-1}, and cyno function at 2215 cm^{-1} and the ^1H NMR spectrum showed absorption bands at δ 8.38 ppm for NH, δ 7.37 and 6.58 for two NH_2 and at δ 1.15 and 4.20 ppm corresponding to the ethyl ester group, which were in agreement with its structure.

4. Conclusion

In conclusion, a series of new heterocyclic derivatives of condensed pyrazolopyrimidine, pyrazoloquinazoline and pyrazolotriazine derivatives starting with the cyclic amidine **4a** were synthesized. The structures of the newly synthesized compounds were established on the basis of their spectral data (IR, ^1H NMR, ^{13}C NMR, Mass) and elemental analyses.

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