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UTILITY OF CYANOACETAMIDES AS PRECURSORS TO PYRAZOLO-[3,4-*d*]PYRIMIDIN-4-ONES, 2-ARYL-6-SUBSTITUTED 1,2,3-TRIAZOLO-[4,5-*d*]PYRIMIDINES AND PYRAZOLO[1,5-*a*]PYRIMIDINE-3-CARBOXAMIDES

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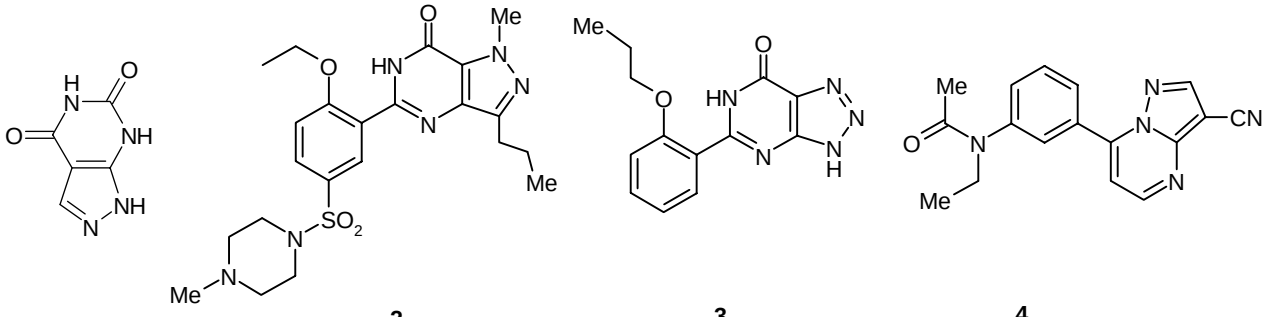
Abstract - Cyanoacetamides (**7a-c)** were prepared *via* reacting cyanoacetic acid **(5)** with amines in the presence of acetic anhydride. Compounds (**7a-c)** coupled with benzenediazonium chloride to yield the phenylhydrazones (**8a-c)**. These reacted with chloroacetonitrile to yield aminopyrazolecarboxamides (**11a-c)**. Reaction of (**8a,b)** with hydroxylamine hydrochloride in DMF in presence of anhydrous sodium acetate afforded the amino-1,2,3-triazolecarboxamides (**36a,b)**. Also compounds (**7a-c)** reacted with dimethylformamide dimethylacetal (DMFDMA) to yield the enamines (**9a-c)** which react with hydrazine hydrate to afford the aminopyrazoles (**16a-c).** Compounds (**16)** and **(36)** reacted with DMFDMA to yield the title heterocyclic derivatives.

INTRODUCTION

Azolopyrimidines are biologically interesting molecules and their chemistry is receiving a considerable interest.[1-4] For example allopurinol (**1)** is established as a medicament for treatment gouty arthritis[5-7] while sildenafil (**2)** and zaprinsat (**3)** are known to be potent and selective phosphodiesterase type 5 (PDE-5) inhibitors which are extensively utilized for treatment of male erectile dysfunction.[8-11] On the other hand, zaleplon (**4)** is well accepted drug for treatment of insomnia.[12-14]

Derivatives of (**1-4)** are efficiently obtained utilizing azoleamines as starting materials.[15-17] Recently, we developed several new efficient synthetic procedures for azoleamines utilizing simple, readily obtainable

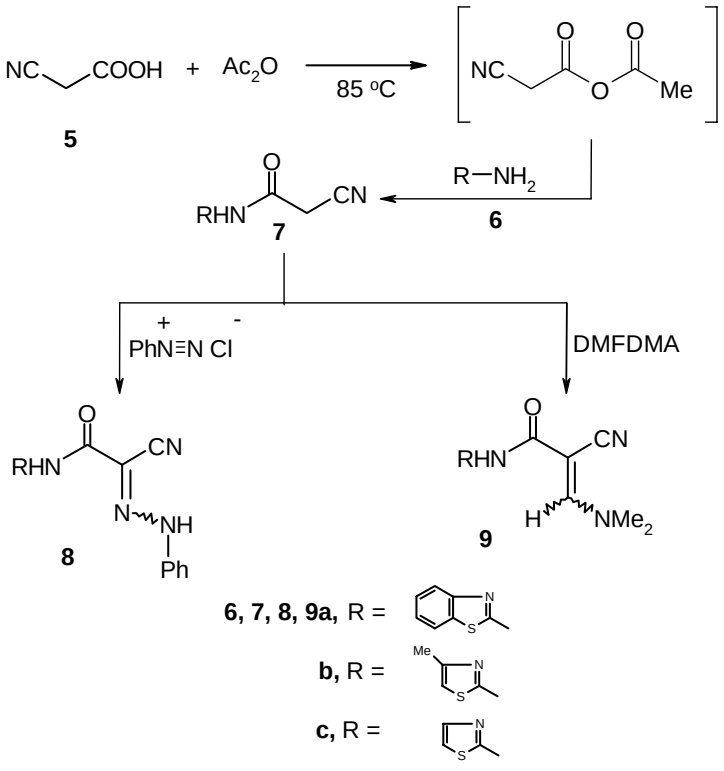
arylhydrazononitriles[18-20] as well as enaminonitriles.[21]



1 **2** **3** **4**

RESULTS AND DISCUSSION

In conjunction of this work, we report here the synthesis of cyanoacetamides **(7a-c)** and their utility for the synthesis of the targeted molecules. Thus, treatment of heterocyclic amines (**6a-c)** with cyanoacetic acid (**5)** in acetic anhydride afforded cyanoacetyl derivatives (**7a-c)** that revealed low field NH proton typical for secondary amide NH. Compound (**5)** would be initially converted into a mixed anhydride and then acylate the heteroaromatic amines.[22, 23]



5 **7** **6** **8** **9**

6, 7, 8, 9a, R =

b, R =

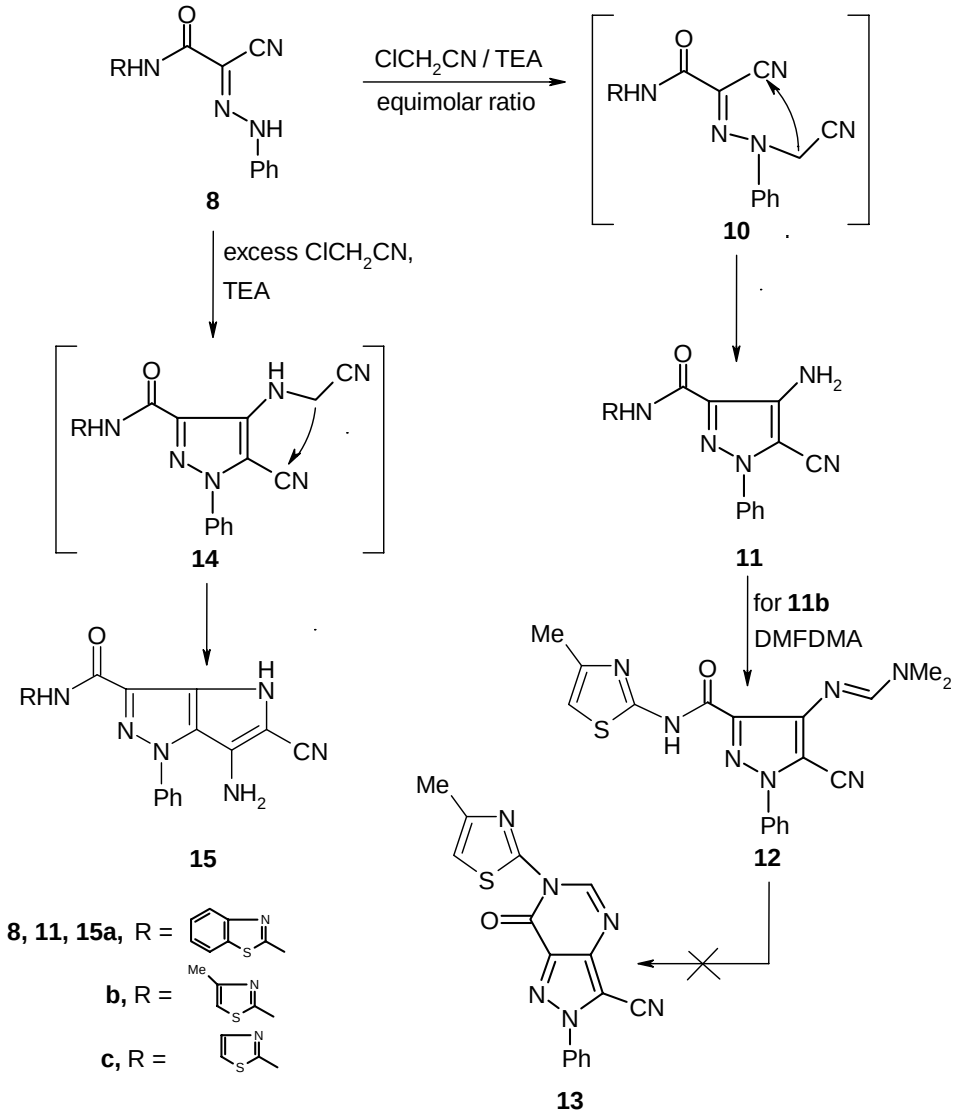
c, R =

Scheme 1

Compounds (**7a-c)** readily coupled with benzenediazonium chloride to yield the corresponding phenylhydrazones (**8a-c)** for which exact stereochemistry seemed difficult to define as we have recently shown that stereoelectronic factors in several cases overweigh the potential fixation by hydrogen

bonding.[24, 25] Although (**8c)** was proved pure by TLC, its ^{13}C NMR revealed 20 carbons instead of the expected 10 carbons, the extra carbons which appear in the ^{13}C NMR of (**8c)** are attributed to the presence of two or more isomeric forms at least under the measured conditions. Compounds (**7a-c)** also reacted with dimethylformamide dimethylacetal (DMFDMA) to yield the enamines (**9a-c)** in good yields. Enaminonitriles (**9a-c)** can exist either in E or Z configuration or as a mixture of both, the ^{1}H NMR indicated presence of only one isomer. While it is most likely that E form is preferred as in this form the molecule would experience least steric interactions, the Z form can not be totally excluded based on the present data and spectral data seems to be of little help in discriminating both forms (Scheme 1).

Compounds (**8)** and (**9)** could be readily utilized as precursors to azolopyrimidines by adopting our recently reported methodology for the synthesis of 4-aminopyrazoles,[18, 21] 5-amino-1,2,3-triazoles[26] and 5-aminopyrazoles.[27] Thus compounds (**8a-c)** reacted with chloroacetonitrile in equimolar ratio to give the

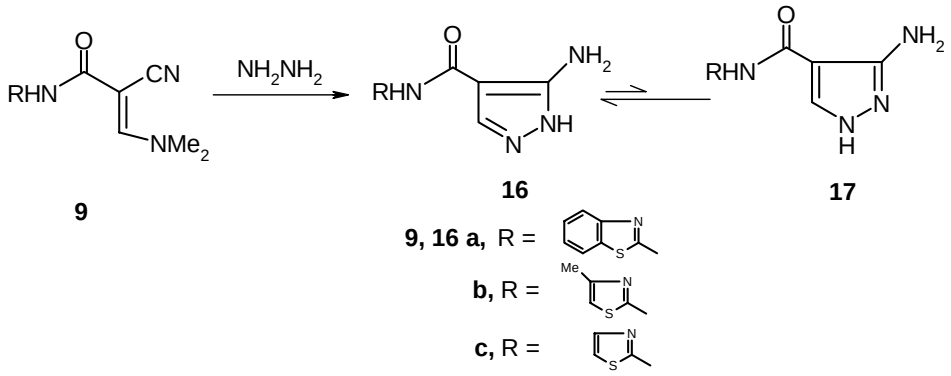


Scheme 2

Aminopyrazoles (**11a-c)** *via* the cyanomethylated hydrazones (**10a-c),** whose structure is supported by the absence of methylene proton signal at δ 3-5 ppm. Intermediates (**10a-c)** are initially formed and then

cyclized under the reaction conditions to the corresponding aminopyrazoles.[18] This demonstrates the general nature of this reaction that, enable synthesis of otherwise not readily obtainable 4-amino-1-arylpyrazoles. Compound (**11)** reacted with DMFDMA to provide (**12)** which did not cyclize into the pyrazolopyrimidine (**13)**. When compounds (**8a,b)** were reacted with an excess of chloroacetonitile, it afforded (**15a,b)** presumably *via* an intermediacy (**14)** (Scheme 2).

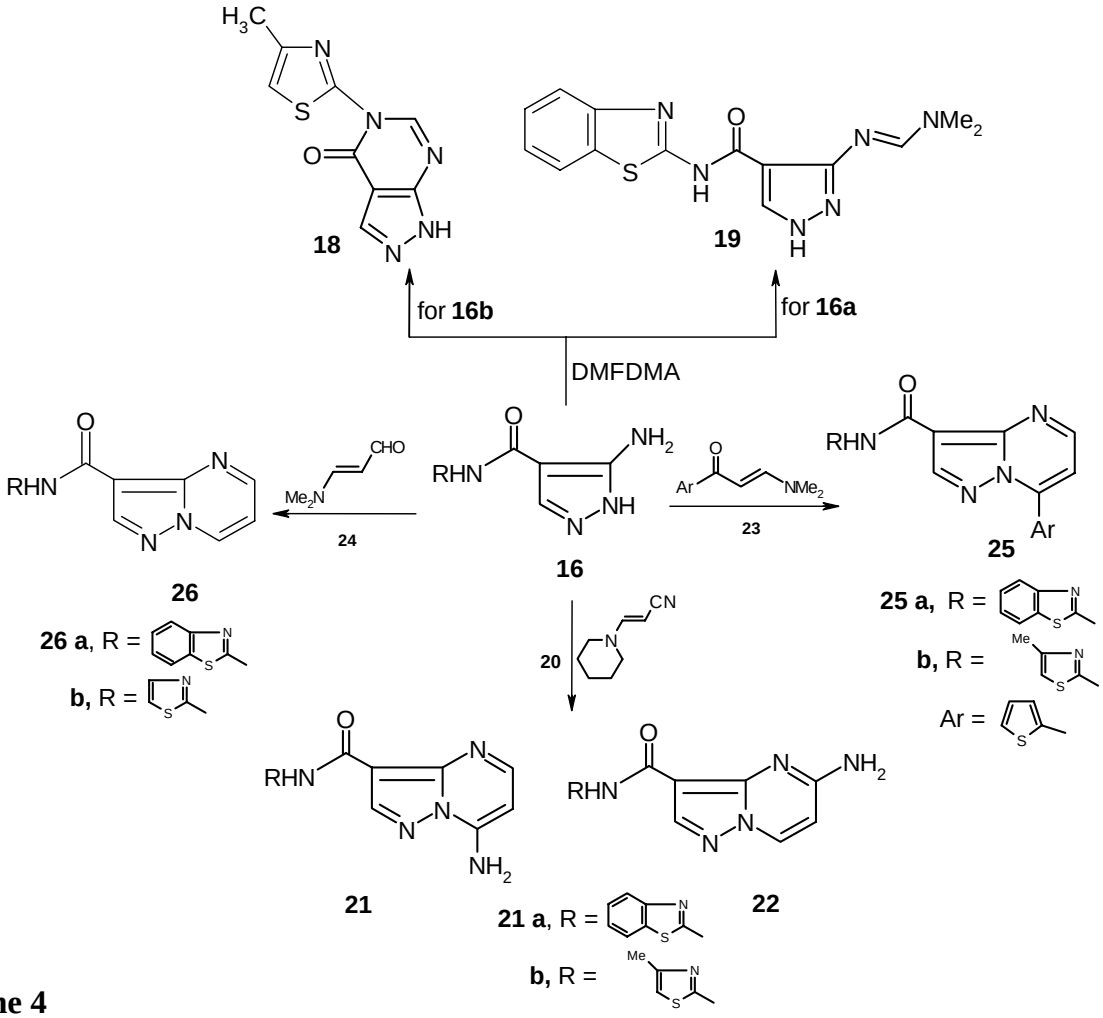
Compounds (**9a-c)** reacted with hydrazine hydrate to yield pyrazoles (**16)**. Inspection of ^{1}H NMR enabled establishing structure (**16)** for these pyrazoles derivatives since the pyrazole H-3 appeared as a singlet at δ 8.0-8.3 ppm, we could not trace in the^{1}H NMR any signals for the tautomeric **(17)** as this would reveals pyrazole H-5 as doublt (Scheme 3).



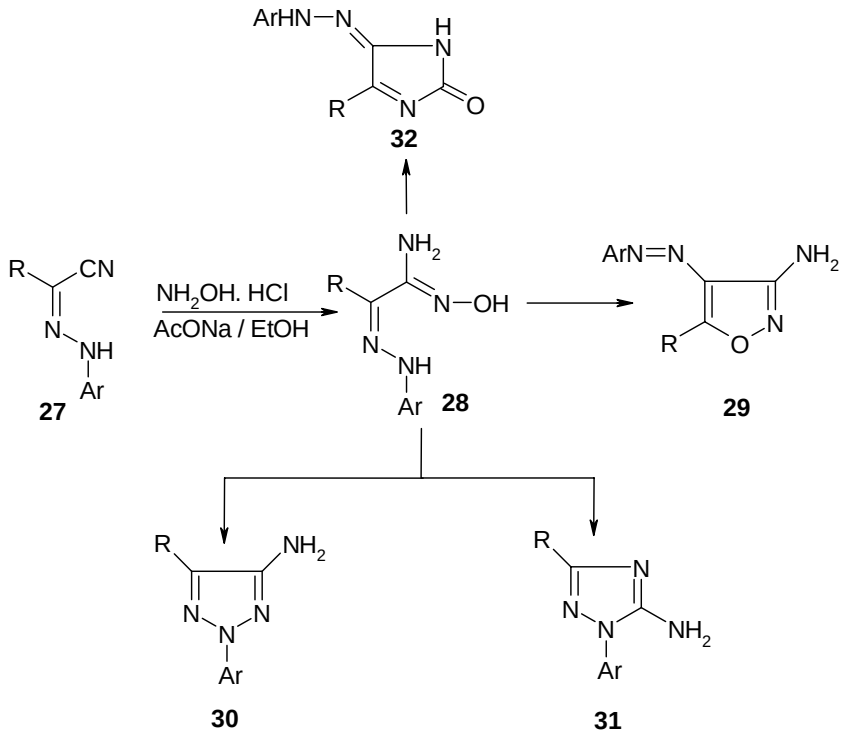
Scheme 3

Compound (**16b)** reacted with DMFDMA to give the pyrazolo[4,3-*d*]pyrimidine (**18)** while (**16a)** provide (**19)** which did not further cyclized to the corresponding pyrazolopyrmidine. Although **(19)** may be presented in the 1*H*-5-amino form the 1*H*-3-amino form was established based on the ^{1}H NMR that revealed H-5 as doublet at δ 8.89. The Reaction of (**16a,b)** with (**20)** afforded the 7-amino-pyrazolo[1,5-*a*]pyrimidine (**21),** whose C-6 appeared at δ ~ 92 ppm typical to the C-6 in 7-aminopyrazolo[1,5-*a*]pyrimidine.[16] Although some 5-aminopyrazolo[1,5-*a*]pyrimidines are known[28] ^{13}C NMR for such derivatives has not been reported to enable comparison however C-6 in 5-aminopyrazolo[1,5-*a*]pyrimidine should resonate at lower fields as it is not affected by amino lone pair resonance. Compound (**16)** also reacted with the enaminone (**23)** and with the enaminal (**24)** to yield the pyrazolo[1,5-*a*]pyrimidinecarboxamide (**25)** and (**26)**, respectively (Scheme 4).

It has been shown earlier that arylhydazononitriles (**27)** react with hydroxylamine hydrochloride to yield the amidoximes (**28)** which could be cyclized into isoxazoles the (**29)**, 1,2,3-triazoleamines (**30)**, 1,2,4-triazoleamines (**31)** or imidazoles (**32)** depending on the applied reaction conditions and the nature of substituent R.[26,29] When R is acetyl or under acidic condition, the isooxazoles (**29)** are formed while in basic media cyclization affords either 1,2,3-triazoleamines (**30)** or 1,2,4-triazoleamines (**31)** *via* a rare Beckman like rearrangement (Tieman rearrangement).[30] Formation of imidazoles **(32)** from (**28)** (R= COPh) with thionyl chloride has also been reported in the old literature[31] (Scheme 5).

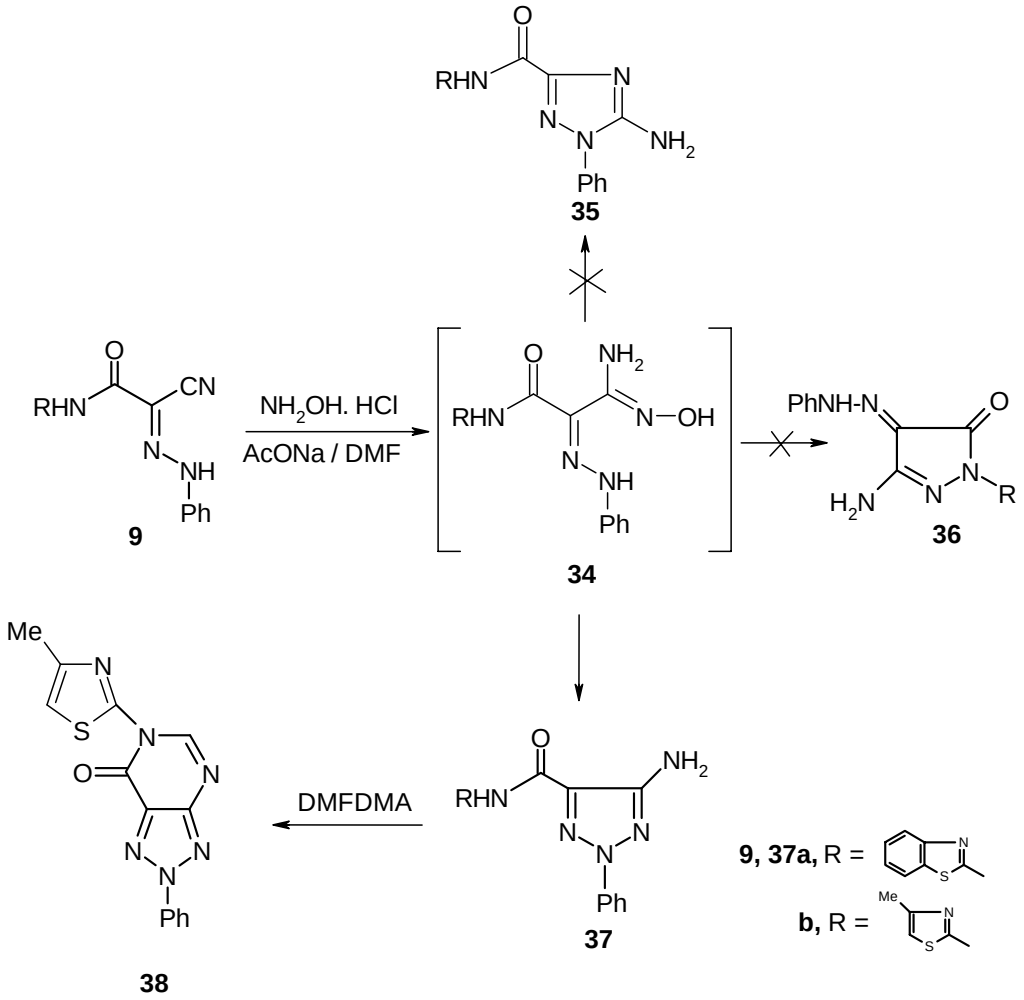


Scheme 4



Scheme 5

Now it has been found that **(8a,b)** reacts with hydroxylamine hydrochloride in anhydrous DMF in the presence of anhydrous sodium acetate to provide an amidoxime intermediate (**33),** which further cyclized to the 1,2,3-triazoles (**36a,b).** The condensation of compound (**36b**) with DMFDMA afforded the triazolo[4,5-*d*]pyrimidine (**37)** (Scheme 6).



Scheme 6

Conclusion

In conclusion cyanoacetic acid reacted with amines in acetic anhydride to yield cyanoacetamides in good yields. Cyanoacetamides were proved to be excellent precursors to aminopyrazolecarboxamides and aminotriazolecarboxamides that readily afford azolopyrimidines with biological and medicinal interest.

EXPERIMENTAL

General Remarks

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer.^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer in $CDCl_3$ or DMSO-d_6 as a solvent and TMS as internal standard; chemical shifts are reported in δ scale. Mass spectra were measured on a VG

Autospec-Q spectrometer and shimadzu GCMS-QP 1000 EX spectrometer at 70 eV. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer.

General procedure for the preparation of compounds (7a-c).

A solution of cyanoacetic acid **(5)** (10 mmol) in Ac_2O (10 mL) was heated on a water bath for 10 min. Then, the appropriate heteroaromatic amines **(6a-c)** were added to the reaction mixture and the heating continued under reflux for further 15 min. The reaction mixture was left to cool and poured onto cooled water. The solid product so formed was collected by filtration, recrystallized from the appropriate solvent and identified as (7**a-c).**

***N*-(Benzothiazol-2-yl)-2-cyanoacetamide (7a).**

Recrystallized from EtOH/dioxane as creamy white crystals, yield: 2.1 g (97%), mp 220 ^{o}C; IR (KBr): 3288 (NH), 2261 (CN), 1688 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 4.14 (s, 2H, CH_2), 7.29-8.01 (m, 4H, Ar-H) and 12.74 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 27.3 (CH_2), 116.0 (CN), 121.5, 122.6, 124.7, 127.1, 132.3, 149.1, 158.4 (Ar-C) and 163.8 (CO); ms (EI): m/z (%) 217 (M^+, 31.93), 218 (M^++1, 4.6). Anal. Calcd for $C_{10}H_7N_3OS$ (217.25): C, 55.29; H, 3.25; N, 19.34; S, 14.76. Found: C, 55.48; H, 3.32; N, 19.20; S, 14.74.

***N*-(4-Methylthiazol-2-yl)-2-cyanoacetamide (7b).**

Recrystallized from EtOH as creamy white crystals, yield: 1.6 g (88%), mp 160-162 ^{o}C; IR (KBr): 3291 (NH), 2261 (CN), 1676 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 6.82 (s, 1H, thiazolyl H) and 12.38 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 27.0 (CH_2), 116.3 (CN), 109.3, 147.8, 157.8 (thiazole carbons) and 162.7 (CO); ms (EI): m/z (%) 181 (M^+, 21.3), 182 (M^++1, 3.9). Anal. Calcd for $C_7H_7N_3OS$ (181.22): C, 46.40; H, 3.89; N, 23.19; S, 17.69. Found: C, 46.37; H, 3.94; N, 23.28; S, 17.60.

***N*-(Thiazol-2-yl)-2-cyanoacetamide (7c).**

Recrystallized from EtOH/dioxane as creamy white crystals, yield: 1.4 g (84%), mp 223 ^{o}C; IR (KBr): 3436 (NH), 2259 (CN), 1693 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 4.04 (s, 2H, CH_2), 7.29 (d, J = 3.57 Hz, 1H, thiazolyl H), 7.50 (d, J = 3.57 Hz, 1H, thiazolyl H) and 12.47 (br, 1H, NH). ms (EI): m/z (%) 167 (M^+, 34.9), 168 (M^++1, 9.43). Anal. Calcd for $C_6H_5N_3OS$ (167.19): C, 43.10; H, 3.01; N, 25.13; S, 19.18. Found: C, 43.26; H, 3.13; N, 25.19; S, 19.28.

General method for the preparation of compounds (8a-c).

To a stirred solution of (**7a-c)** (10 mmol) in EtOH/dioxane (1:1, 30 mL each) containing NaOAc (10 g) was added the benzenediazonium chloride (prepared from 10 mmol of aniline and the appropriate quantities of sodium nitrite and hydrochloric acid). The solid product separated on standing was filtered off and recrystallized from the appropriate solvent.

***N*-(Benzothiazol-2-yl)(phenylhydrazono)-2-cyanoacetamide (8a)**.

Recrystallized from EtOH/dioxane mixture as yellow crystals, yield: 2.8 g (87 %), mp 238 ^{o}C; IR (KBr): 3391, 3201 (2 NH), 2216 (CN), 1678 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 7.28-7.90 (m, 9H, Ar-H), 9.50 (br, 1H, NH) and 13.97 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 107.0 (C2), 116.3 (CN), 111.9, 117.8, 121.1, 122.6, 124.6, 125.8, 127.2, 129.9, 130.4, 132.3, 142.7 (Ar-C) and 161.9 (CO); ms (EI): m/z (%) 321 (M^+, 75.8), 322 (M^++1, 15.5). Anal. Calcd for $C_{16}H_{11}N_5OS$ (321.36): C, 59.80; H, 3.45; N, 21.79; S, 9.98. Found: C, 59.71; H, 3.48; N, 21.75; S, 9.89.

***N*-(4-Methylthiazol-2-yl)(phenylhydrazono)-2-cyanoacetamide (8b).**

Recrystallized from EtOH as orange crystals, yield: 2.4 g (85 %), mp 190-192 ^{o}C; IR (KBr): 3230, 3192 (2 NH), 2218 (CN), 1697 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.60 (s, 1H, thiazolyl H), 7.19-7.58 (m, 5H, Ar-H), 9.44 (br, 1H, NH) and 13.95 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 17.8 (CH_3), 108.1 (thiazole C-5), 109.1 (C2), 116.1 (CN), 117.7, 125.4, 125.7, 130.1, 130.6, 143.0 (Ar-C and thiazole carbons) and 161.9 (CO); ms (EI): m/z (%) 285 (M^+, 52.5), 286 (M^++1, 13.1). Anal. Calcd for $C_{13}H_{11}N_5OS$ (285.33): C, 54.72; H, 3.89; N, 24.54; S, 11.24. Found: C, 54.60; H, 3.82; N, 24.35; S, 11.30.

(Phenylhydrazono)-*N*-(thiazol-2-yl)-2-cyanoacetamide (8c).

Recrystallized from EtOH/dioxane as orange crystals, yield: 2.2 g (81 %), mp 259 ^{o}C; IR (KBr): 3435, 3371 (2 NH), 2218 (CN), 1667 cm-1 (CO); ^{1}H NMR (DMSO-d_6): δ 7.16 (t, J = 7.9 Hz, 1H, Ar-H), 7.29 (d, J = 3.6 Hz, 1H, thiazolyl H), 7.40 (t, J = 7.9 Hz, 2H, Ar-H), 7.56 (d, J = 3.6 Hz, 1H, thiazolyl H), 7.85 (d, J = 8.0 Hz, 2H, Ar-H), 12.37 (br, 1H, NH) and 14.08 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 107.3, 112.1, 113.5, 113.6, 114.9, 116.1, 117.8, 118.5, 125.3, 125.7, 126.1, 130.0, 130.5, 138.4, 142.6, 142.9, 159.3, 161.2, 168.0 and 169.7 (Ar-C, thiazole carbons and CO); ms (EI): m/z (%) 271 (M+, 100), 272 (M^++1, 21.76). Anal. Calcd for $C_{12}H_9N_5OS$ (271.30): C, 53.13; H, 3.34; N, 25.81; S, 11.82. Found: C, 53.19; H, 3.42; N, 25.63; S, 11.64.

General procedure for the preparation of compounds (9a-c).

A mixture of (**7a-c)** (10 mmol) and DMFDMA (1.2 g, 10 mmol) in dioxane (30 mL) was refluxed for 4 h. Then the solvent was reduced to one third of its volume under reduced pressure, and the reaction mixture was allowed to cool down to rt. The solid product obtained on standing was collected by filtration and crystallized from the appropriate solvent.

(*E*)-*N*-(Benzothiazol-2-yl)-2-cyano-3-(dimethylamino)acrylamide (9a).

Recrystallized from dioxane as creamy white crystals. yield: 2.3 g (84 %), mp 232-234 ^{o}C; IR (KBr): 3405 (NH), 2189 (CN), 1679 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 3.24 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 7.23-7.91 (m, 4H, Ar-H), 8.05 (s, 1H, olefinic CH) and 11.72 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 39.6 (CH_3), 48.2 (CH_3), 72.5 (C2), 119.5 (CN), 120.1, 122.7, 123.9, 124.2, 127.1, 131.8, 148.4, 157.7 (Ar-C

and olefinic C) and 161.07 (CO) ms (EI): m/z (%) 272 (M^+, 35.3), 273 (M^++1, 11.24). Anal. Calcd for $C_{13}H_{12}N_4OS$ (272.33): C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.37; H, 4.51; N, 20.53; S, 11.75.

(*E*)-2-Cyano-3-(dimethylamino)-*N*-(4-methylthiazol-2-yl)acrylamide (9b).

Recrystallized from EtOH as buff crystals. yield: 2.1 g (89 %), mp 228 ^oC; IR (KBr): 3104, (NH), 2190 (CN), 1672 cm^{-1} (CO). ^1H NMR ($CDCl_3$): δ 2.36 (s, 3H, thiazolyl CH_3), 3.28 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.51 (s, 1H, thiazolyl H), 7.91 (s, 1H, olefinic CH) and 9.07 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 17.7 (thiazolyl CH_3), 39.3 (CH_3), 48.5 (CH_3), 71.9 (C-2), 108.6 (thiazole C-5), 118.9 (CN), 147.9 (thiazole C-4), 157.7 (olefinic C), 158.0 (thiazole C-2) and 163.1 (CO); ms (EI): m/z (%) 236 (M^+, 13.2), 237 (M^++1, 4.1). Anal. Calcd for $C_{10}H_{12}N_4OS$ (236.30): C, 50.83; H, 5.12; N, 23.71; S, 13.57. Found: C, 50.91; H, 5.06; N, 23.82; S, 13.56.

(*E*)-2-Cyano-3-(dimethylamino)-*N*-(thiazol-2-yl)acrylamide (9c).

Recrystallized from EtOH/dioxane as pale yellow crystals. yield: 1.6 g (72 %), mp 215 ^oC; IR (KBr): 3435 (NH), 2187 (CN), 1656 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ 3.19 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 7.11 (d, 1H, J = 3.65 Hz, thiazolyl H), 7.43 (d, J = 3.65 Hz, 1H, thiazolyl H), 8.0 (s, 1H, olefinic CH) and 11.41 (br, 1H, NH); ms (EI): m/z (%) 222 (M^+, 35.5), 223 (M^++1, 8.3). Anal. Calcd for $C_9H_{10}N_4OS$ (222.27): C, 48.63; H, 4.53; N, 25.21; S, 14.43. Found: 48.54; H, 4.60; N, 25.36; S, 14.39.

General method for the preparation of compounds (11a-c).

Equimolar amounts of chloroacetonitrile and (**8a-c)** (5 mmol) in Et_3N (15 mL) were refluxed for 30 min. Then, the reaction mixture was allowed to cool to rt. The obtained residual product was triturated with methanol to give a solid product which collected by filtration, washed with water and recrystallized from the appropriate solvent.

4-Amino-*N*-(benzothiazol-2-yl)-5-cyano-1-phenyl-1*H*-pyrazole-3-carboxamide (**11a).**

Recrystallized from EtOH as yellow crystals, yield: 1.3 g (72 %), m.p. 272-274 ^oC; IR (KBr): 3441, 3357, 3170 (NH_2 and NH), 2216 (CN), 1645 (CO), 1539 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 5.71 (s, 2H, NH_2), 7.19-8.10 (m, 9H, Ar-H) and 13.77 (br, 1H, NH); ^{13}C NMR (DMSO- d_6): δ 116.9 (CN) 113.3, 113.8, 117.1, 124.8, 124.9, 125.5, 126.3, 126.5, 129.2, 130.4, 130.6, 136.0, 142.3, 168.4, (Ar-C) and 169.4 (CO); ms (EI): m/z (%) 360 (M^+, 38.9), 361 (M^++1, 10.9). Anal. Calcd for $C_{18}H_{12}N_6OS$ (360.40): C, 59.99; H, 3.36; N, 23.32; S, 8.90. Found: C, 59.89; H, 3.50; N, 23.27; S, 8.79.

4-Amino-5-cyano-*N*-(4-methylthiazol-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (11b).

Recrystallized from EtOH as yellow crystals, yield: 1.25 g (77 %), mp 242 ^oC; IR (KBr): 3457, 3356, 3136 (NH_2 and NH), 2218 (CN), 1595 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 5.43 (s, 2H, NH_2), 6.34 (s, 1H, thiazolyl H), 7.15-7.73 (m, 5H, Ar-H) and 13.78 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.3 (CH_3), 106.7 (thiazole C-5), 116.1 (CN), 116.5 (pyrazole C-5), 123.5, 125.8, 129.8, 130.6, 130.7,

135.2, 144.8, 168.4 (Ar-C) and 169.1 (CO); ms (EI): m/z (%) 324 (M^+, 23.3), 325 (M^++1, 6.4). Anal. Calcd for $C_{15}H_{12}N_6OS$ (324.37): C, 55.54; H, 3.73; N, 25.91; S, 9.89. Found: C, 55.67; H, 3.75; N, 25.84; S, 9.81.

4-Amino-5-cyano-1-phenyl-*N*-(thiazol-2-yl)-1*H*-pyrazole-3-carboxamide (11c).

Recrystallized from dioxane as yellow crystals, yield: 1.15 g (74 %), mp 270 ^oC; IR (KBr): 3457, 3422, 3149 (NH_2 and NH), 2216 (CN), 1597 cm^{-1} (CO); ^1H NMR (DMSO- d_6): δ 5.46 (s, 2H, NH_2), 7.17 (t, J = 8.0 Hz, 1H, Ar-H), 7.34 (d, J = 3.7 Hz, 1H, thiazolyl H), 7.42 (t, J = 8.0 Hz, 2H, Ar-H), 7.47 (d, J = 8.0 Hz, 2H, Ar-H), 7.82 (d, J = 3.7 Hz, 1H, thiazolyl H) and 13.74 (br, 1H, NH); ms (EI): m/z (%) 309 (M^+, 48.65), 325 (M^++1, 13.7). Anal. Calcd for $C_{14}H_{10}N_6OS$ (310.34): C, 54.18; H, 3.25; N, 27.08; S, 10.33. Found: C, 54.03; H, 3.32; N, 26.88; S, 10.13.

5-Cyano-4-(dimethylaminomethyleneamino)-*N*-(4-methylthiazol-2-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (12).

A mixture of (**11b)** (5 mmol) and DMFDMA (0.6 g, 5 mmol) in dioxane (15 mL) was refluxed for 4h. Then, the reaction mixture was poured into ice cold water and the formed solid product was collected by filtration and recrystallized from EtOH as orange crystals; yield: 1.2 g (63 %), mp 124 ^oC; IR (KBr): 3137, (NH), 2218 (CN), 1646 cm^{-1} (CO). ^1H NMR (DMSO- d_6): δ 1.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 6.48 (s, 1H, thiazolyl H), 7.12-7.34 (m, 5H, Ar-H), 7.46 (s, 1H, imino CH) and 14.14 (br, 1H, NH); m/z (%) 379 (M^+, 39.3), 380 (M^++1, 18.1). Anal. Calcd for $C_{18}H_{17}N_7OS$ (379.45): C, 56.98; H, 4.52; N, 25.84; S, 8.45. Found: C, 57.09; H, 4.38; N, 25.73; S, 8.40.

General method for the preparation of compounds (15a, b).

A mixture of (**8a,b)** (5 mmol) and chloroacetonitrile (1.2 g, 15 mmol) in Et_3N (15 mL) were refluxed for 30 min. Then, the reaction mixture was allowed to cool down to rt. The obtained residual product was triturated with ethanol to give a solid product, which collected by filtration, washed with water and recrystallized from the appropriate solvent.

6-Amino-*N*-(benzothiazol-2-yl)-5-cyano-1,4-dihydro-1-phenylpyrrolo[3,2-*c*]pyrazole-3-carboxamide (15a).

Recrystallized from EtOH/dioxane as yellow crystals, yield: 1.35 g (68 %), mp 268 ^oC; IR (KBr): 3462, 3351, 3238, 3180 (NH_2 and 2NH), 2219 (CN), 1631 (CO), 1587 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 5.52 (s, 2H, NH_2), 7.15-7.83 (m, 10H, Ar-H and NH) and 14.11 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 112.2 (CN), 111.6, 116.4, 122.9, 124.0, 124.1, 125.9, 126.2, 126.3, 128.5, 129.0, 129.5, 130.2, 130.2, 135.1, 141.8, 167.8, (Ar-C) and 170.7 (CO); ms (EI): m/z (%) 399 (M^+, 100), 400 (M^++1, 24.1). Anal. Calcd for $C_{20}H_{13}N_7OS$ (399.44): C, 60.14; H, 3.28; N, 24.55; S, 8.03. Found: C, 60.22; H, 3.41; N, 24.52; S, 7.92.

6-Amino-5-cyano-1,4-dihydro-*N*-(4-methylthiazol-2-yl)-1-phenylpyrrolo[3,2-*c*]pyrazole-3-carboxamide (15b).

Recrystallized from EtOH/dioxane as yellow crystals, yield: 1.1 g (60 %), m.p. 257 °C; IR (KBr): 3456, 3354, 3285, 3104 (NH_2 and 2NH), 2217 (CN), 1670 (CO), 1595 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 5.43 (s, 2H, NH_2), 6.85 (s, 1H, thiazolyl H), 7.42-7.74 (m, 6H, Ar-H and NH) and 13.79 br, 1H, NH); ms (EI): m/z (%) 399 (M^+, 100), 400 (M^++1, 24.1). Anal. Calcd for $C_{17}H_{13}N_7OS$ (363.40): C, 56.19; H, 3.61; N, 26.98; S, 8.82. Found: C, 55.99; H, 3.72; N, 27.08; S, 8.75.

General procedure for the preparation of compounds (16a-c).

A mixture of the enamine **(9a-c)** (10 mmol), and hydrazine hydrate (0.5 ml, 10 mmol) in dioxane (20 mL) was refluxed for 3 h. The reaction mixture was allowed to cool down to rt and then poured into ice cold water. The crude product was then collected by filtration washed with water and crystallized from the appropriate solvent.

5-Amino-*N*-(benzothiazol-2-yl)1*H*-pyrazole-4-carboxamide (16a).

Recrystallized from dioxane as buff crystals. yield: 2.0 g (77 %), mp 286-88 °C; IR (KBr): 3443, 3348, 3262, 3166 (NH_2 and 2NH), 1662 (CO), 1600 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 6.24 (s, 2H, NH_2), 7.28 (t, J = 8.0 Hz, 1H, Ar-H), 7.43 (t, J = 8.0 Hz, 1H, Ar-H), 7.72 (d, J = 7.9 Hz, 1H, Ar-H), 7.95 (d, J = 7.9 Hz, 1H, Ar-H), 8.21(s, 1H, pyrazole H-3), 11.96 (br, 1H, NH) and 12.14 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 96.5 (pyrazole C-4), 121.0, 122.5, 122.9, 124.2, 124.8, 127.0, 132.6, 138.7, 149.7, 154.5, 159.7 (Ar-C), 163.3 (CO) (EI): m/z (%) 259 (M^+, 25.5), 260 (M^++1, 8.1). Anal. Calcd for $C_{11}H_9N_5OS$ (259.29): C, 50.96; H, 3.50; N, 27.01; S, 12.37. Found: C, 60.08; H, 3.55; N, 26.98; S, 12.25.

5-Amino-*N*-(4-methylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (16b).

Recrystallized from EtOH/dioxane as creamy white crystals. yield: 1.9 g (85 %), mp 276 °C; IR (KBr): 3440, 3349, 3238, 3187 (NH_2 and 2 NH), 1665 (CO), 1618 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 6.08 (s, 2H, NH_2), 6.68 (s, 1H, thiazolyl H), 8.15 (s, 1H, pyrazole H-3) and 11.84 (br, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 96.8 (pyrazole C-4), 108.0 (thiazole C-5), 138.4, 147.3, 153.6, 158.9 (Ar-C), 162.8 (CO); ms (EI): m/z (%) 223 (M^+, 22.1), 224 (M^++1, 6.8). Anal. Calcd for $C_8H_9N_5OS$ (223.26): C, 43.04; H, 4.06; N, 31.37; S, 14.36. Found: C, 42.89; H, 4.12; N, 31.46; S, 14.42.

5-Amino-1*H*-pyrazole-*N*-(thiazol-2-yl)-4-carboxamide (16c).

Recrystallized from EtOH/dioxane as creamy white crystals. yield: 1.6 g (77 %), mp 212 °C; IR (KBr): 3448, 3353, 3183, 3126 (NH_2 and 2NH), 1653 (CO), 1621 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 6.15 (s, 2H, NH_2), 7.15 (d, J = 3.6 Hz, 1H, thiazolyl H), 7.47 (d, J = 3.6 Hz, 1H, thiazolyl H), 8.15 (s, 1H, pyrazole H-3) and 11.90 (br, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 97.0 (pyrazole C-4), 113.8 (thiazole C-5), 137.1 (pyrazole C-3), 138.4 (thiazole C-4), 154.5 (pyrazole C-5), 159.6 (thiazole C-2), 162.8 (CO); ms (EI): m/z (%) 209 (M^+, 28.4), 210 (M^++1, 12.8). Anal. Calcd for $C_7H_7N_5OS$ (209.23): C, 40.18; H, 3.37; N, 33.47; S, 15.32. Found: 40.07; H, 3.50; N, 33.39; S, 15.21.

General procedure for the preparation of compounds (18, 19).

A mixture of (**16a,b) (**5 mmol) and DMFDMA (0.6 mL, 5 mmol) in anhydrous DMF (15 mL) was refluxed for 5 h. Then, the reaction mixture was allowed to cool to rt then poured into ice cold water containing few drops from hydrochloric acid then the crude product was collected by filtration washed with water and crystallized from the appropriate solvent.

5-(4-Methylthiazol-2-yl)-1,5-dihydropyrazolo[3,4-*d*]pyrimidine-4-one (18).

Recrystallized from EtOH as orange crystals, yield: 0.9 g (77 %), mp 177 ^{o}C; IR (KBr): 3183 (NH), 1701 cm^{-1}(CO); ^{1}H NMR (DMSO-d_6):δ 2.26 (s, 3H, CH_3), 5.56 (s, 1H, thiazolyl H), 6.72 (s, 1H, H-6), 8.26 (s, 1H, H-3) and 12.05 (br, H, NH); ms (EI): m/z (%) 233 (M^+, 43.1 %), 234 (M^++1, 12.5%). Anal. Calcd for $C_9H_7N_5OS$ (233.25): C, 46.34; H, 3.02; N, 30.02; S, 13.75. Found: C, 46.45; H, 2.98; N, 29.89; S, 13.66.

(*E*)-*N*-(benzothiazol-2-yl)-3-[(Dimethylamino)methyleneamino]-1*H*-pyrazole-4-carboxamide (19).

Recrystallized from EtOH/dioxane as creamy white crystals, yield: 1.0 g (63 %), mp 297 ^{o}C; IR (KBr): 3432, 3202 (2NH), 1687 (CO), 1599 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 7.36 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.54 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.91 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.33 (s, 1H, imino CH), 8.89 (d, *J* = 11.0 Hz, 1H, pyrazolyl H), 9.75 (br, 1H, NH) and 11.12 (br, 1H, NH); ms (EI): m/z (%) 314 (M+, 12.5 %). Anal. Calcd for $C_{14}H_{14}N_6OS$ (314.37): C, 53.49; H, 4.49; N, 26.73; S, 10.20. Found: C, 53.40; H, 4.38; N, 26.84; S, 10.06.

General procedure for the preparation of compounds (21).

A mixture of **(16a,b)** (10 mmol), and (**20)** (1.36 g, 10 mmol) in pyridine (20 mL) was refluxed for 7 h. The reaction mixture was allowed to cool to rt and poured into ice cold water, then acidified with hydrochloric acid. The formed crude solid product was collected by filtration, washed with water and recrystallized from the appropriate solvent.

7-Amino-*N*-(benzothiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21a).

Recrystallized from dioxane as pale brown crystals, yield: 2.5 g (81%), mp above 300 ^{o}C; IR (KBr): 3465, 3314, 3176 (NH_2 and NH), 1648 (CO), 1600 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 6.43 (d, *J* = 5.5 Hz, 1H, H-6), 7.33 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.46 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.01 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.42 (d, 1H, *J* = 5.5 Hz, H-5), 8.55 (br, 2H, NH_2), 8.71 (s, 1H, H-2) and 11.89 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 92.5 (C-6), 101.4, 121.4, 122.8, 124.5, 127.2, 132.7, 146.2, 148.9, 149.6, 150.4, 152.6, 158.4 (Ar-C) and 160.6 (CO); ms (EI): m/z 310 (M^+, 34.35 %), 311 (M^++1, 9.81 %). Anal. Calcd for $C_{14}H_{10}N_6OS$ (310.34): C, 54.18; H, 3.25; N, 27.08; S, 10.33. Found: C, 54.06; H, 3.32; N, 26.96; S, 10.22.

7-Amino-*N*-(4-methylthiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21b).

Recrystallized from EtOH/dioxane as pale brown crystals, yield: 2.0 g (73 %), mp 228 ^{o}C; IR (KBr): 3424, 3313, 3120 (NH_2 and NH), 1659 (CO), 1599 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 6.48 (d,

J = 6.0 Hz, 1H, H-6), 6.82 (s, 1H, thiazolyl H), 8.31 (d, *J* = 6.0 Hz, 1H, H-5), 8.82 (s, 1H, H-2), 9.35 (br, 2H, NH_2), and 12.13 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 16.7 (CH_3), 92.1 (C-6), 100.9, 107.6, 144.6, 145.6, 147.0, 150.6, 157.7, 159.5 (Ar-C) and 161.6 (CO); ms (EI): m/z 274 (M^+, 17.7 %), 275 (M^++1, 6.5 %). Anal. Calcd for $C_{11}H_{10}N_6OS$ (274.31): C, 48.17; H, 3.67; N, 30.64; S, 11.69. Found: C, 48.06 H, 3.82; N, 30.78; S, 11.71.

General procedure for the preparation of compounds (25).

A mixture of **(16a,b)** (10 mmol) and enaminone (**23)** (1.81 g, 10 mmol) in pyridine (20 mL) was refluxed for 6 h. The reaction mixture was allowed to cool to rt and poured onto ice cold water, then acidified with hydrochloric acid. The formed crude solid product was collected by filtration, washed with water and crystallized from the appropriate solvent.

***N*-(Benzothiazol-2-yl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (25a).**

Recrystallized from dioxane/DMF as yellow crystals, yield: 2.9 g (78 %), mp above 300 °C; IR (KBr): 3289 (NH), 1684 (CO), 1599 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 7.34 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.46-7.50 (m, 2H, Ar-H and thiophene H), 7.81 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.04 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.13 (d, *J* = 3.7 Hz, 1H, thiophene H), 8.26 (d, *J* = 5.0 Hz, 1H, H-6), 8.67 (d, *J* = 3.7 Hz, 1H, thiophene H), 9.01 (d, *J* = 5.0 Hz, 1H, H-5), 9.05 (s, 1H, H-2) and 11.80 (br, 1H, NH); ms (EI): m/z 377 (M^+, 28.9 %), 378 (M^++1, 9.5 %). Anal. Calcd for $C_{18}H_{11}N_5OS_2$ (377.45): C, 57.28; H, 2.94; N, 18.55; S, 16.99. Found: C, 57.33; H, 3.04; N, 18.64; S, 17.11.

***N*-(4-Methylthiazol-2-yl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (25b).**

Crystallized from dioxane/DMF as pale yellow crystals, yield: 2.7 g (79 %), mp 273 °C; ; IR (KBr): 3241 (NH), 1660 (CO), 1598 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 2.9 (s, 3H, CH_3), 6.82 (s, 1H, thiazolyl H), 7.44 (t, *J* = 4.0 Hz, 1H, thiophene H), 8.08 (d, *J* = 5.0 Hz, 1H, H-6), 8.23 (d, *J* = 4.0 Hz, 1H, thiophene H), 8.64 (d, *J* = 4.0 Hz, 1H, thiophene H), 8.94 (d, *J* = 5.0 Hz, 1H, H-5), 9.00 (s, 1H, H-2) and 11.50 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.9 (CH3), 103.8 (thiazole C-5), 107.2 (C-3), 109.2 (C-6), 129.3, 130.2, 134.8, 137.5, 142.4, 146.7, 147.9, 148.1, 153.0, 157.6 (Ar-C) and 159.5 (CO) ; ms (EI): m/z 341 (M^+, 22.8 %), 342 (M^++1, 4.5 %). Anal. Calcd for $C_{15}H_{11}N_5OS_2$ (341.42): C, 52.77; H, 3.25; N, 20.51; S, 18.78. Found: C, 52.83; H, 3.31; N, 20.65; S, 18.82.

General procedure for the preparation of compounds (26).

A mixture of (**16a,c)** (10 mmol) and enaminal (**24)** (1.0 g, 10 mmol) in pyridine (20 mL) was refluxed for 6 h. Then, the solvent was evaporated under reduced pressure, and the remaining residue was triturated with MeOH to afford crystals, which were then collected by filtration and recrystallized from the appropriate solvent.

***N*-(Benzothiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26a).**

Recrystallized from dioxane/DMF as pale brown crystals, yield: 2.2 g (75 %), mp 298 °C; IR (KBr): 3251 (NH), 1677 (CO), 1618 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 7.33 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.42-7.48 (m, 2H, Ar-H and H-6), 7.78 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.02 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.90 (s, 1H, H-2), 9.00 (d, *J* = 5.7 Hz, 1H, H-5), 9.44 (d, *J* = 5.7 Hz, 1H, H-7) and 11.64 (br, 1H, NH);^{13}C NMR (DMSO-d_6): δ 103.8 (C-3), 112.0 (C-6), 121.5, 122.9, 124.7, 127.3, 132.7, 139.3, 147.2, 147.4, 149.5, 154.7, 158.4 (Ar-C) and 160.2 (CO) ms (EI): m/z 295 (M^+, 37.8 %), 296 (M^++1, 7.9 %). Anal. Calcd for $C_{14}H_9N_5OS$ (295.32): C, 56.94; H, 3.07; N, 23.71; S, 10.86. Found: C, 57.08; H, 2.92; N, 23.80; S, 10.89.

***N*-(Thiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26b).**

Recrystallized from dioxane/DMF as pale brown crystals, yield: 1.9 g (78 %), mp 248 °C; IR (KBr): 3268 (NH), 1675 (CO), 1617 cm-1 (C=N); ^{1}H NMR (DMSO-d_6): δ 7.28 (d, *J* = 3.6 Hz, 1H, thiazolyl H), 7.41 (t, *J* = 6.0 Hz, 1H, H-6), 7.52 (d, *J* = 3.6 Hz, 1H, thiazolyl H), 8.84 (s, 1H, H-2), 8.97 (d, *J* = 6.0 Hz, 1H, H-5), 9.42 (d, *J* = 6.0 Hz, 1H, H-7) and 11.41 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 103.5 (C-3), 111.7 (C-6), 114.8 (thiazole C-5), 138.6, 139.0, 146.8, 147.0, 154.3, 158.2 (Ar-C) and 159.4 (CO); ms (EI): m/z 245 (M^+, 24.2 %), 246 (M^++1, 7.3 %). Anal. Calcd for C10H7N5OS (245.26): C, 48.97; H, 2.88; N, 28.55; S, 13.07. Found: 49.10; H, 2.96; N, 28.65; S, 12.98.

General procedures for Preparation of compounds (36a,b).

A mixture of the phenylhydrazones (**8a,b)** (10 mmol), hydroxylamine (10 mmol), and anhydrous NaOAc (3 g) in anhydrous DMF (20 ml) was refluxed for 3 h. The reaction mixture was allowed to cool to rt and poured into ice cold water, and the crude product was collected by filtration, washed with water and recrystallized from the appropriate solvent.

5-Amino-*N*-(benzothiazol-2-yl)-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide (36a).

Recrystallized from dioxane as pale brown crystals yield: 1.9 g (57 %), mp 182-84 °C; IR (KBr): 3451, 3390, 3250 (NH_2 and NH), 1661(CO), 1617 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 6.31 (s, 2H, NH_2), 7.33-8.08 (m, 5H, Ar-H) and 12.73 (br, 1H, NH); ms (EI): m/z (%) 336 (M^+, 14.8), 337 (M^++1, 3.26). Anal. Calcd for $C_{16}H_{12}N_6OS$ (336.38): C, 57.13; H, 3.60; N, 24.98; S, 9.53. Found: C, 57.21; H, 3.56; N, 24.88; S, 9.46.

5-Amino-*N*-(4-methyl-thiazol-2-yl)-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide (36b).

Recrystallized from EtOH/dioxane as pale brown crystals yield: 2.0 g (66 %), mp 139 °C; IR (KBr): 3454, 3439, 3232 (NH2 and NH), 1661 (CO), 1618 cm-1 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, CH3), 6.22 (s, 2H, NH2), 6.82 (s, 1H, thiazolyl H), 7.38-8.04 (m, 5H, Ar-H) and 12.41 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.6 (CH3), 108.8 (thiazole C-5), 117.1, 124.4, 128.5, 130.0, 130.3, 130.6, 139.9, 156.0, (Ar-C) and 161.1 ppm (CO); ms (EI): m/z (%) 300 (M^+, 35.8), 301 (M^++1, 8.8). Anal. Calcd for

$C_{13}H_{12}N_6OS$ (300.34): C, 51.99; H, 4.03; N, 27.98; S, 10.68. Found: C, 51.85; H, 4.11; N, 28.07; S, 10.72.

2,5-Dihydro-5-(4-Methylthiazol-2-yl)-2-phenyl-1,2,3-triazolo[4,5-*d*]pyrimidine-4-one (37).

A mixture of (**36b)** (1.5 g, 5 mmol) and DMFDMA (0.6 g, 5 mmol) in anhydrous DMF (15 mL) was refluxed for 5 h. Then, the reaction mixture was allowed to cool to rt and poured over ice cold water the formed solid product was collected by filtration and recrystallized from dioxane as pale brown crystals, yield: 1.6 g (53 %), mp 151 ^oC; IR (KBr): 1690 (CO), 1628 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 6.90 (s, 1H, thiazolyl H), 7.29-8.17 (m, 5H, Ar-H) and 8.57 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 109.5 (thiazole C-5), 119.0, 123.2, 129.9. 130.6, 132.4, 139.9, 148.2, 156.0, 157.3 (Ar-C) and 159.9 (CO); ms (EI): m/z (%) 310 (M^+, 18.5), 311 (M^++1, 5.8). Anal. Calcd for $C_{14}H_{10}N_6OS$ (310.34): C, 54.18; H, 3.25; N, 27.08; S, 10.33. Found: C, 53.99; H, 3.14; N, 26.92; S, 10.21.

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