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Hetarylcyanamides: Synthesis of Novel Thiazole, Triazole and Pyrimidine Derivatives and Prediction of their Biological Activity *via* PASS Inet

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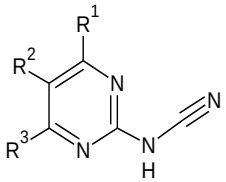
Abstract: Some new *N*-thiazolylaminopyrimidine derivatives **3a,b** have been synthesized *via* the reaction of 1-(4,6-dimethylpyrimidin-2-yl)thiourea **2**, obtained *via* sulfidation of cyanamide **1a** with phenacyl bromides. Acid hydrolysis of *N*-(pyrimidin-2-yl)cyanamides **1b,c** gave the corresponding pyrimidinylurea derivatives **4a,b**. Reaction of cyanamide **1b** with thieno[2,3-*b*]thiophene derivative **5**, at molar ratios (1:1 or 2:1), gave the unexpected thienopyrimidine derivative **6**, not the expected *bis*-thienopyrimidine derivative **7**. Triazolylaminopyrimidine derivative **8** has been obtained *via* the heterocyclization reaction of cyanamide **1b** with benzhydrazide. Prediction the activity spectra of synthesized compounds using PASS Inet at Pa > 70%, showing high probability of Mucomembranous protector, Transcription factor STAT inhibitor and Gluconate 2-dehydrogenase (acceptor) inhibitor.

Keywords: Hetarylcyanamide, Aminothiazole, Thienopyrimidine, Aminotriazole, PASS Inet.

1 Introduction

Hetarylcyanamides having both nucleophilic nitrogen atom of the amino group and electrophilic carbon atom of the nitrile group can undergo reactions with a wide range of reagents [1,3]. They are capable of electrophilic substitution at the amino group [4] or nucleophilic addition and cycloaddition at the triple bond of the nitrile group [2]. These chemical properties have been utilized to construct of some heterocyclic moiety such as benzazoles [5,6], triazoles [7,8], tetrazoles [5], oxadiazoles [9] and pyrimidines [10]. Some of these heterocycles have diverse biological activities including anti-inflammatory [11], antifungi [12], antidiabetic [13] and anticancer [14] activities.



1a-c

a: R^1 = Me, R^2 = H, R^3 = Me

b: R^1 = H, R^2 = COOEt, R^3 = Ph

c: R^1 = H, R^2 = H, R^3 = *p*-MeOPh

Figure 1

In continuation of our program for synthesis of some novel fused heterocycles [15,16], we aimed to use *N*-(pyimidin-2-yl)cyanamides **1a-c** (*see* figure 1) as building block for the synthesis of thiazole, triazole and pyrimidine derivatives with the hope to possess important biological activity.

2 Results and Discussion

2.1 Chemistry

N-(4,6-Dimethylpyrimidin-2-yl)cyanamide **1a** [17] has been reported to react with hydrogen sulphide, in presence of triethylamine as catalyst, to give 1-(4,6-dimethylpyrimidin-2-yl)thiourea **2** [18,19]. Substituted thiourea **2** was reacted with phenacyl bromides to give the corresponding *N*-thiazolylaminopyrimidine derivatives **3a,b**, (Scheme 1). The reaction was preceded *via* treatment of thiourea **2** with sodium methoxide to form sodium salt, which consequently was reacted in pot with phenacyl bromides, in dimethylformamide. The resulting *S*-phencylated intermediate **I**, which in turn underwent an intramolecular cyclization, leading to products **3a,b**, (Scheme 1).

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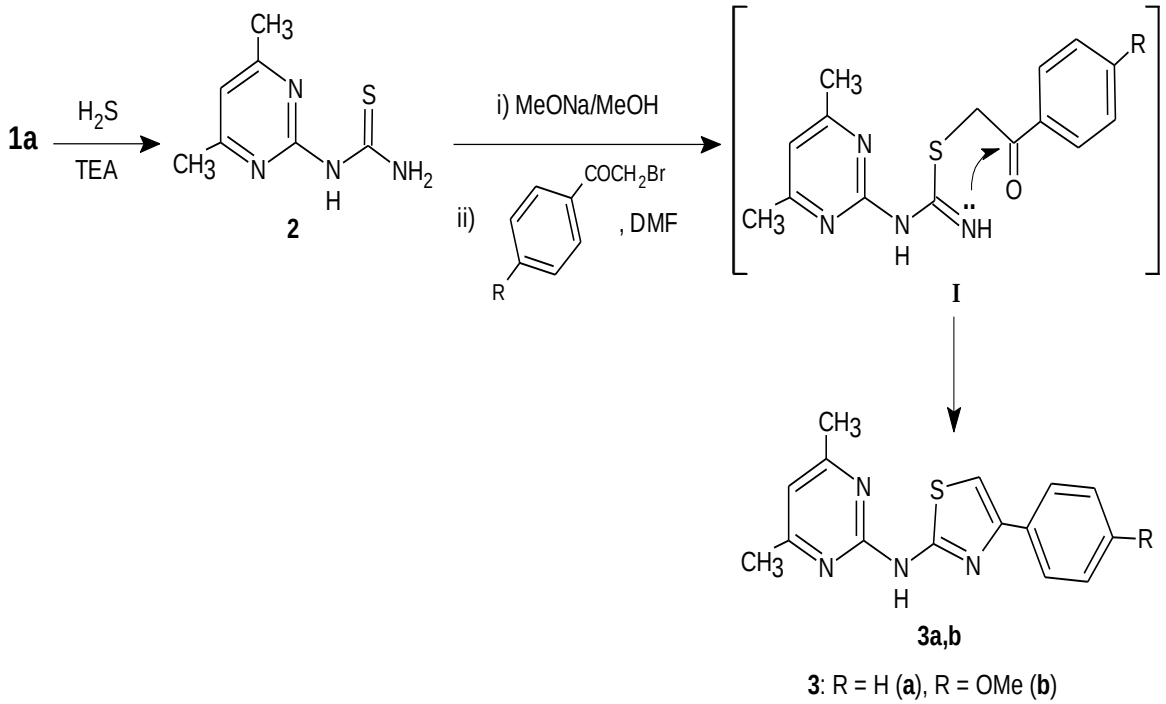
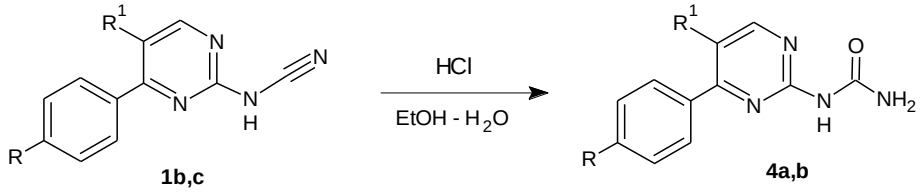


Scheme 1

The structure of the newly synthesized compounds **3a,b** was confirmed by their spectra IR, ^{1}H, ^{13}C NMR and elemental analyses. For example, IR spectrum of compound **3a** showed disappearance of characteristic absorption band for NH_2 group, while exhibited characteristic absorption bands at $\bar{\upsilon}$ 3304 cm^{-1} (N-H). ^{1}H NMR spectrum showed one singlet signal at δ 2.42 characteristic for two CH_3, multiplet aromatic signals at δ 7.31-7.92 and broad singlet signal at δ 11.38 due to NH group (disappeared by D_2O). ^{13}C NMR spectrum showed ten signals which are assigned to aromatic carbons at δ 167.7, 160.2, 157.3, 149.5, 135.3, 129.0, 127.9, 126.2, 113.1, 107.5; one signal in aliphatic region at δ 23.7 due to CH_3.

Cyano group of cyanamides **1b,c** was easily acid hydrolyzed, in aqueous ethanol solution, in the presence of catalytic amounts of hydrochloric acid, to give the corresponding pyrimidinylurea derivatives **4a,b**, (Scheme 2). The hydrolysis process was carried out through formation of chloroformamidine intermediate [20,21].



1b, 4a: R = H, R^1 = COOEt; **1c, 4b**: R = OMe, R^1 = H

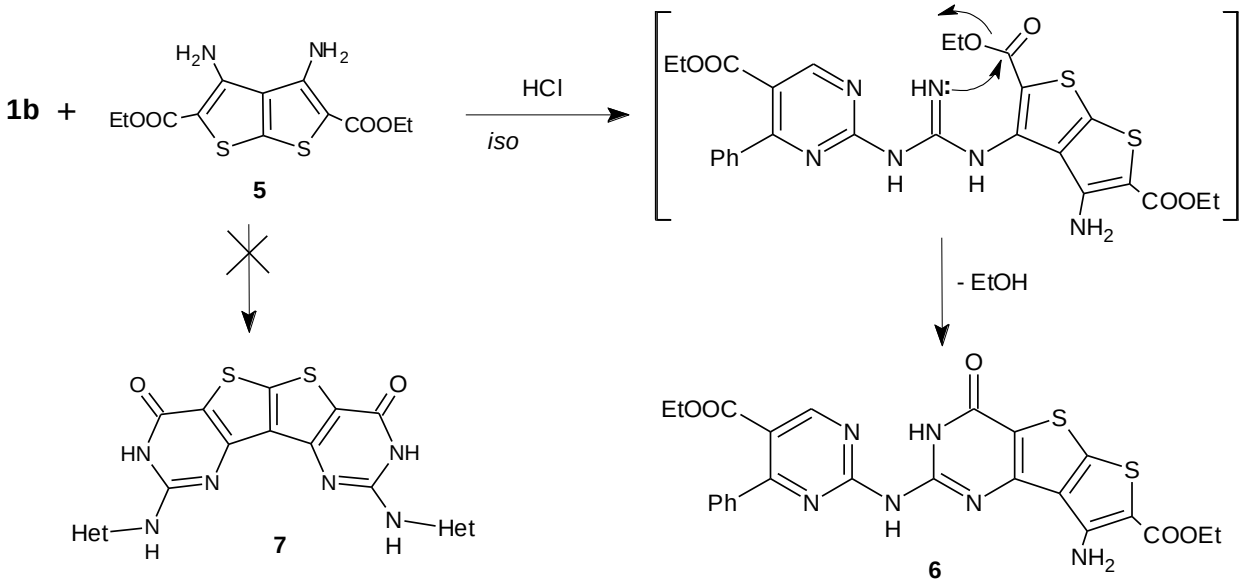
Scheme 2

IR spectrum of compound **4a** showed disappearance of CN group and exhibited absorption bands at ῡ 3372, 3149 and 3109 cm^{-1} characteristic for NH_2, NH groups; and 1704, 1662 cm^{-1} due to ester and amidic carbonyl groups, respectively. ^1H NMR spectrum showed two singlet signals at δ 8.95 and 10.14 due to CH pyrimidine ring and NH group, respectively (NH disappeared by D_2O); two broad singlet signals at δ 7.28 and 8.40 for NH_2 group protons (disappeared by D_2O); triplet and quartet signals at δ 1.05, 4.13 for protons of ethyl ester set.

Reacting a mixture of cyanamide **1b** and diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate (**5**), at molar ratios (1:1 or 2:1), in presence of HCl in boiling *iso*-propanol, led to the unexpected thienopyrimidine derivative **6** and not the expected *bis*-thienopyrimidine **7**, (Scheme 3).

The formation of product **6** may be attributed to its precipitation through the reaction. The plausible mechanism for the formation of **6** was assumed to proceed *via* first formation of guanidine adduct intermediate, which consequently underwent an intramolecular cyclization *via* an addition-elimination process.

IR spectrum of product **6** showed no evidence for presence of CN group, and exhibited characteristic absorption bands at ῡ 3457, 3441 and 3346 cm^{-1} for NH and NH_2 groups; and 1726, 1673 cm^{-1} due to C=O ester and amidic groups, respectively. ^1H NMR spectrum showed appearance of four singlet signals at δ 6.75, 9.08, 11.86 and 13.01 due to NH_2, $CH_{pyrimidine}$, $NH_{pyrimidine}$ and NH, respectively, (2NH, NH_2 disappeared by D_2O).



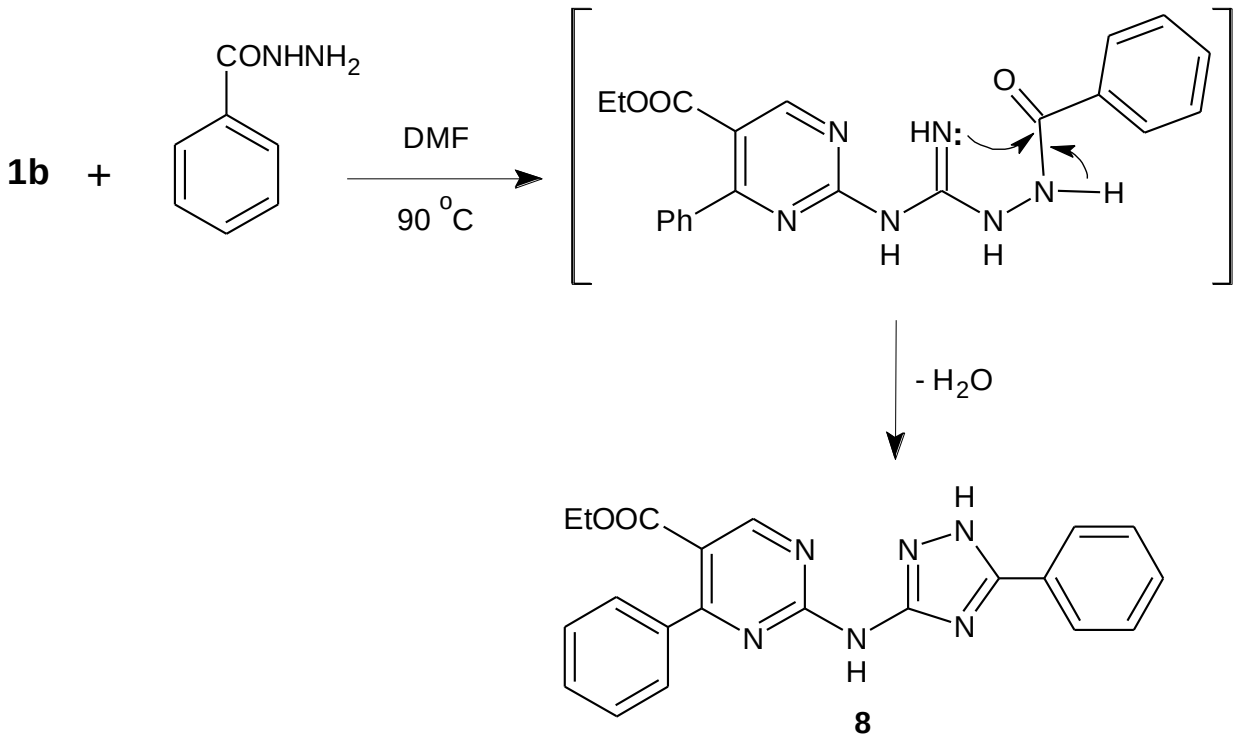
7: Het = ethyl 4-phenylpyrimidin-2-yl-5-carboxylate

Scheme 3

Reaction of cyanamide **1b** with benzhydrazide, in hot DMF at 90 °C, gave triazolyaminopyrimidine **8**, (Scheme 4). It is thought that reaction might pass through first formation of aminoguanidine intermediate, which can be cyclized *via* an addition-elimination process, (Scheme 4).
IR spectrum of compound **8** exhibited absorption band at ῡ 1725 cm-1 ($C=O_{ester}$); and ^1H NMR spectrum showed two singlet signals corresponding to CH pyrimidine and NH group at δ 8.86 and 10.33, respectively (NH disappeared by D_2O); multiplet signals at δ 7.46 - 7.95 for ten aromatic protons and NH group (NH disappeared by D_2O); triplet and quartet signals at δ 1.05, 4.10 for protons of ethyl ester set. ^{13}C NMR spectrum showed fourteen signals at δ 165.9, 160.4, 158.7, 145.4, 145.2, 139.0, 138.2, 131.9, 129.9, 129.1, 128.8, 128.6, 128.4 and 128.1, which are assigned to aromatic carbons; one signal at δ 166.9 ($C=O_{ester}$); and signals in aliphatic region of CH_2 and CH_3 groups at δ 60.9 and 14.1, respectively.

2.2 Biological Activity Predicted by PASS Inet

The biological activity spectra for all new six synthesized compounds **3a,b**, **4a,b**, **6** and **8** were obtained by PASS database internet site [22]. The prediction of biological activity, using PASS database was carried out based on analysis of training set containing about 46,000 drugs and biologically active compounds. This set consider as reference compounds for known chemical compounds as well as different biological activities. It estimates the probability of the molecule to be active (Pa) and inactive (Pi) for each type of activity from the biological activity spectrum. Interpretation of prediction results is based on consideration of Pa values [23,24].



Scheme 4

Here in we represented the percent activity (Pa) and inactivity (Pi) of our products in table 1, when Pa > 0.7 so the chance of finding activity experimentally is high and in many cases the compound may be a close analogue of known pharmaceutical agents.

According to these data the most frequently predicted types of biological activities are *Mucomembranous protector*, *Transcription factor STAT inhibitor* and *Gluconate 2-dehydrogenase (acceptor) inhibitor*.

But when 0.5 < Pa < 0.7, the chance of finding activity experimentally is less and the compound is not so similar to known pharmaceutical agents. Table 2 represented the probability of activity (Pa) and inactivity (Pi) of the new products.

3 Experimental

3.1 General

All melting points were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as Brucker Alpha Fourier Transform (FT-IR). ^{1}H NMR and ^{13}C NMR spectra (chemical shift δ) were recorded on a Bruker at 400 and 100 MHz, respectively using TMS as an internal reference and DMSO-d_6 as a solvent. The elemental analyses were carried out on a Perkin-Elmer 2400 CHNS/O Microanalyzer. All compounds were checked for their purity on TLC plates. Compounds **1a** [17], **1b,c** [25] and **2** [18,19] were prepared according to literature described methods.

Table 1. Biological activity predicted by PASS for Pa > 7.0

Compound No.	***Activities***	***Pa***	***Pi***
3a	Mucomembranous protector	0.749	0.035
	Transcription factor STAT inhibitor	0.705	0.004
3b	Transcription factor STAT inhibitor	0.717	0.004
4b	Gluconate 2-dehydrogenase (acceptor) inhibitor	0.733	0.039

Table 2. Biological activity predicted by PASS for 0.5 < Pa < 0.7

Compound No.	*Activities*	*Pa*	*Pi*
3a	Transcription factor STAT3 inhibitor	0.616	0.006
	Transcription factor inhibitor	0.611	0.005
	EIF4E expression inhibitor	0.601	0.003
	5 Hydroxytryptamine release inhibitor	0.601	0.011
	Antiulcerative	0.575	0.013
	Insulin promoter	0.531	0.024
	Thioredoxin inhibitor	0.537	0.045
	Complement factor D inhibitor	0.537	0.057
	Taurine dehydrogenase inhibitor	0.530	0.078
3b	Transcription factor STAT3 inhibitor	0.641	0.005
	Transcription factor inhibitor	0.623	0.005
	Mucomembranous protector	0.666	0.072
	5 Hydroxytryptamine release inhibitor	0.584	0.013
	Antiulcerative	0.565	0.014
	EIF4E expression inhibitor	0.504	0.010
	Ubiquinol-cytochrome-c reductase inhibitor	0.522	0.141
	Aspulvinone dimethylallyltransferase inhibitor	0.505	0.135
4a	Transcription factor inhibitor	0.642	0.004
	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor	0.616	0.040
	tRNA-pseudouridine synthase I inhibitor	0.589	0.017
	Cytokine production inhibitor	0.576	0.004
	Antiviral (Picornavirus)	0.579	0.024
	Transcription factor NF kappa B inhibitor	0.555	0.004
	Fragilysin inhibitor	0.577	0.032
	Hematopoietic inhibitor	0.532	0.009
	Anesthetic general	0.513	0.020
	Lysostaphin inhibitor	0.503	0.029
	Oxidoreductase inhibitor	0.529	0.064
	Fibrinolytic	0.533	0.107
	Membrane permeability inhibitor	0.521	0.135
4b	Antiallergic	0.646	0.012
	Antiasthmatic	0.634	0.013
	Antiarthritic	0.639	0.023
	Cytokine production inhibitor	0.592	0.004
	Fructose 5-dehydrogenase inhibitor	0.603	0.019
	Para amino benzoic acid antagonist	0.563	0.005
	Nicotine dehydrogenase inhibitor	0.529	0.020
	TNF expression inhibitor	0.528	0.024
	2-Hydroxyquinoline 8-monooxygenase inhibitor	0.517	0.047
	CDP-glycerol glycerophosphotransferase inhibitor	0.558	0.098
	Taurine dehydrogenase inhibitor	0.514	0.084
	Aspulvinone dimethylallyltransferase inhibitor	0.542	0.119
	Ubiquinol-cytochrome-c reductase inhibitor	0.522	0.141
6	Transcription factor inhibitor	0.569	0.007
8	Signal transduction pathways inhibitor	0.600	0.019
	Protein kinase inhibitor	0.588	0.013
	Histidine kinase inhibitor	0.559	0.020
	Histamine release inhibitor	0.551	0.019
	Transcription factor inhibitor	0.537	0.010
	Angiogenesis inhibitor	0.534	0.016

3.2 General Procedure for Reaction of Thiourea 2 with Phenacyl Bromides

Heating of 1-(4,6-dimethylpyrimidin-2-yl)thiourea **2** (5 mmol, 0.91 g) in 60 ml sodium methoxide 0.1 M (0.14 g sodium metal in 60 ml methanol) for 30 min, then the solvent was evaporated under vacuum. The residual was dissolved in 40 ml DMF and the selective reagent (5 mmol): phenacyl bromide (1.0 g) or p-methoxyphenacyl bromide (1.15 g) was added. The reaction mixture was then stirred and heated at 50-60 °C for 8 hrs. After completion of the reaction, the mixture was allowed to cool to room temperature and poured into ice water containing HCl drops. The formed precipitate was collected by filtration, dried, and recrystallized from ethanol.

4,6-Dimethyl-N-(4-phenyl-1,3-thiazol-2-yl)pyrimidin-2-amine (**3a**): Yield 73%; yellow crystal; m.p.: 210-212 °C. IR (ATR) ν_{max} 3304, 3053, 2948, 1595 cm^{-1}. ^1H NMR δ 11.38 (br. s, 1H, NH), 7.91 (d, *j* = 7.4 Hz, 2H, $CH_{arom.}$), 7.42 (m, 3H, $CH_{thiazole}$ + $CH_{arom.}$), 7.31 (m, 1H, $CH_{arom.}$), 6.81 (s, 1H, $CH_{pyrimidine}$), 2.42 (s, 6H, $2CH_3$). ^{13}C NMR δ 167.7, 160.2, 157.3, 149.5, 135.3, 129.0, 127.9, 126.2, 113.1, 107.5, 23.7. Anal. Calcd. for $C_{15}H_{14}N_4S$ (282): C, 63.80; H, 5.00; N, 19.84. Found: C, 63.61; H, 5.15; N, 19.96.

4,6-Dimethyl-N-[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-pyrimidin-2-amine (**3b**): Yield 79%, brown solid; m.p.: 170-172 °C. IR (ATR) ν_{max} 3308, 3045, 2960, 2920, 1597 cm^{-1}. ^1H NMR δ 11.46 (s, 1H, NH), 7.84 (d, 2H, *j* = 8.4 Hz, $2CH_{phenylene}$), 7.30 (s, 1H, $CH_{thiazole}$), 6.98 (d, 2H, *j* = 8.4 Hz, $2CH_{phenylene}$), 6.79 (s, 1H, $CH_{pyrimidine}$), 3.81 (s, 3H, OCH_3), 2.40 (s, 6H, $2CH_3$). ^{13}C NMR δ 167.7, 160.0, 159.3, 157.3, 149.3, 128.1, 127.5, 114.4, 113.0, 105.5, 55.6, 23.7. Anal. Calcd. for $C_{16}H_{16}N_4OS$ (312): C, 61.52; H, 5.16; N, 17.93. Found: C, 61.90; H, 5.08; N, 17.85.

*3.3 General Procedure for Acid Hydrolysis of Cyanamides **1b,c***

Heating of ethyl 2-(cyanoamino)-4-phenylpyrimidine-5-carboxylate **1b** and/or [4-(4-methoxyphenyl)pyrimidin-2-yl]cyanamide **1c** (5 mmol) in 60 ml aqueous ethanol solution with hydrochloric acid (1 ml) for 2 hrs. After completion of the hydrolysis, the mixture was allowed to cool to room temperature, poured into ice-cold distilled water and the solution was then neutralized to pH ~ 7 by using sodium hydroxide solution. The formed precipitate was collected by filtration, dried, and recrystallized from ethanol.

Ethyl2-(carbamoylamino)-4-phenylpyrimidine-5-carboxylate (**4a**)*:* Yield 81%, white solid; m.p.: 152-153°C. IR (ATR) ν_{max} 3372, 3149, 3109, 3062, 2982, 2902, 1704, 1662 cm^{-1}. ^1H NMR δ 10.14 (s, 1H, NH), 8.95 (s, 1H, $CH_{pyrimidine}$), 8.40 (br. s, 1H, NH_2), 7.53 (m, 5H, CH_{phenyl}), 7.28 (br. s, 1H, NH_2), 4.13 (q, *j* = 6.9 Hz, 2H, CH_2), 1.05 (t, *j* = 6.9 Hz, 3H, CH_3). Anal. Calcd. for $C_{14}H_{14}N_4O_3$ (286): C, 58.73; H, 4.93; N, 19.57. Found: C, 58.58; H, 4.99; N, 19.78.

1-[4-(4-Methoxyphenyl)pyrimidin-2-yl]urea (**4b**): Yield 85%, white solid; m.p.: 140-142 °C. IR (ATR) ν_{max} 3326, 3157, 3110, 3077, 2965, 1681 cm^{-1}. ^1H NMR δ 9.83 (s, 1H, NH), 8.55 (d, *j* = 3.9 Hz, 1H, $CH_{pyrimidine}$), 8.13 (d, *j* = 7.8 Hz, 2H, $CH_{phenylene}$), 7.61 (d, *j* = 3.9 Hz, 1H, $CH_{pyrimidine}$), 7.12 (d, *j* = 7.8 Hz, 2H, $CH_{phenylene}$), 5.37 (br. s, 2H, NH_2), 3.87 (s, 3H, OCH_3). Anal. Calcd. for $C_{12}H_{12}N_4O_2$ (244): C, 59.01; H, 4.95; N, 22.94. Found: C, 59.22; H, 4.87; N, 22.83.

*3.4 Procedure for Reaction of Cyanamide **1b** with Diethyl 3,4-diaminothieno[2,3-b] thiophene-2,5-dicarboxylate **5***

A mixture of cyanamide **1b** (3 mmol, 0.8 g) and thieno[2,3-*b*]thiophene **5** (3 mmol, 1.57 g) was refluxed in 60 ml *iso*-propanol in presence of HCl 36 % (1ml) for 3 hrs. The formed precipitate was collected by filtration and dried. The product was neutralized by 50 ml sodium hydroxide solution 5 % and recrystallized from *iso*-PrOH-DMF mixture.

Ethyl 8-amino-4-oxo-2-[(5-carboethoxy-4-phenylpyrimidin-2-yl)amino]-3,4-dihydro-thieno[3',2':4,5]thieno[3,2-d]pyrimidine-7-carboxylate (**6**)*:* Yield 77%, beige solid; m.p.: > 310 °C. IR (ATR) ν_{max} 3457, 3441, 3346, 3060, 2970, 2926, 1726, 1673, 1631 cm^{-1}. ^1H NMR δ 13.01 (s, 1H, NH_{exo}), 11.86 (s, 1H, NH_{endo}), 9.08 (s, 1H, $CH_{pyrimidine}$), 7.65-7.50 (m, 5H, CH_{phenyl}), 6.75 (s, 2H, NH_2), 4.27-4.12 (m, 4H, $2CH_2$), 1.29 (t, *j* = 7.0 Hz, 3H, CH_3), 1.09 (t, *j* = 7.1 Hz, 3H, CH_3). Anal. Calcd. for $C_{24}H_{20}N_6O_5S_2$ (536): C, 53.72; H, 3.36; N, 15.66. Found: C, 53.49; H, 3.31; N, 15.79.

*3.5 Procedure for Reaction of Cyanamide **1b** with Benzhydrazide*

A mixture of cyanamide **1b** (5 mmol, 1.34 g) and benzhydrazide (5 mmol, 0.68 g) was heated at 90 °C for 7 hrs. After completion of the reaction (TLC monitoring), the mixture was allowed to cool to room temperature, poured into ice-cold distilled water containing HCl drops. The formed precipitate was collected by filtration, dried and recrystallized from *iso*-PrOH-DMF mixture.

Ethyl 4-phenyl-2-[(5-phenyl-1H-1,2,4-triazol-3-yl)amino] pyrimidine-5-carboxylate (**8**)*:* Yield 41%, green solid; m.p.: 218-220 °C. IR (ATR) ν_{max} 3267, 3127, 3066, 3042, 2975, 2896, 1725, 1620 cm^{-1}. ^1H NMR δ 10.33 (br. s, 1H, NH), 8.86 (s, 1H, $CH_{pyrimidine}$), 7.95 (d, *j* = 7.6 Hz, 2H, $CH_{arom.}$), 7.57-7.46 (m, 9H, NH + $CH_{arom.}$), 4.10 (q, *j* = 7.0 Hz, 2H, CH_2), 1.05 (t, *j* = 7.0 Hz, 3H, CH_3). ^{13}C NMR δ 166.9, 165.9, 160.4, 158.7, 145.4, 145.2, 139.0, 138.2, 131.9, 129.9, 129.1, 128.8, 128.6, 128.4, 128.1, 60.9, 14.1. Anal. Calcd. for $C_{21}H_{18}N_6O_2$ (386): C, 65.27; H, 4.70; N, 21.75. Found: C, 65.51; H, 4.61; N, 21.93.

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