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**RESEARCH ARTICLE**

# Synthesis, reaction and antimicrobial activity of some pyridinethione derivatives containing benzimidazole nucleus

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## *Abstract*

Cyanopyridinethione derivatives **3a,b** were reacted with active halogen containing compounds in basic medium to afford the corresponding thienopyridine derivatives **4a,b, 5a,b, 6a,b**. 3-Aminothieno[2,3-b]pyridine-2-carbonitrile **4a** was converted to several pyridothienopyrimidin derivatives **10-15**. Aminothienopyridine carbohydrazide **9** was converted to several triazolyl-, oxadiazolyl- and pyrazolyl- derivatives. Finally, compound **9** reacted with cyanoguanidine followed by NaOH to give aminothienopyridin-1,2,4-triazolyl-guanidine **26** which reacted with aromatic aldehydes and aliphatic acids to give the corresponding triazolo[1,5-a][1,3,5]triazin-2-yl)thieno[2,3-b]pyridin-3-amine derivatives **27a,b** and **28a,b** respectively.



## Introduction:

Many naturally and synthetic compounds bearing pyridine scaffold posses interesting biological activities[1-3]. Substituted 3-cyanopyridines are important intermediates in pharmaceuticals and dyes synthesis. Among them, 2-amino-3-cyanopyridine derivatives are well known for their versatile biological activities like antimicrobial[4,5], antifungal[6] and anti-tubercular[7,8]. Also, benzimidazoles are an important class of heterocyclic compounds which have a wide spectrum of biological activities[9-13]. Some benzimidazole derivatives with different pharmacological effects including antifugal[14], anti-HIV[15], antihistaminic[16,17], antihypertensive[18] are in clinical use. Substituted benzimidazole derivatives have found applications in diverse therapeutical areas such as antimicrobial[19-21], antioxidant[22], antiviral[23,24], anti-inflammatory[25] and molluscicidal[26] agents. Furthermore, benzimidazoles showed anticancer activity against DNA topoisomerase[27, 28]. Thus, in view of the above facts, it was of interest to synthesize a ring system combining both the pyridine and the benzimidazole moieties which might have good biological and medicinal applications.

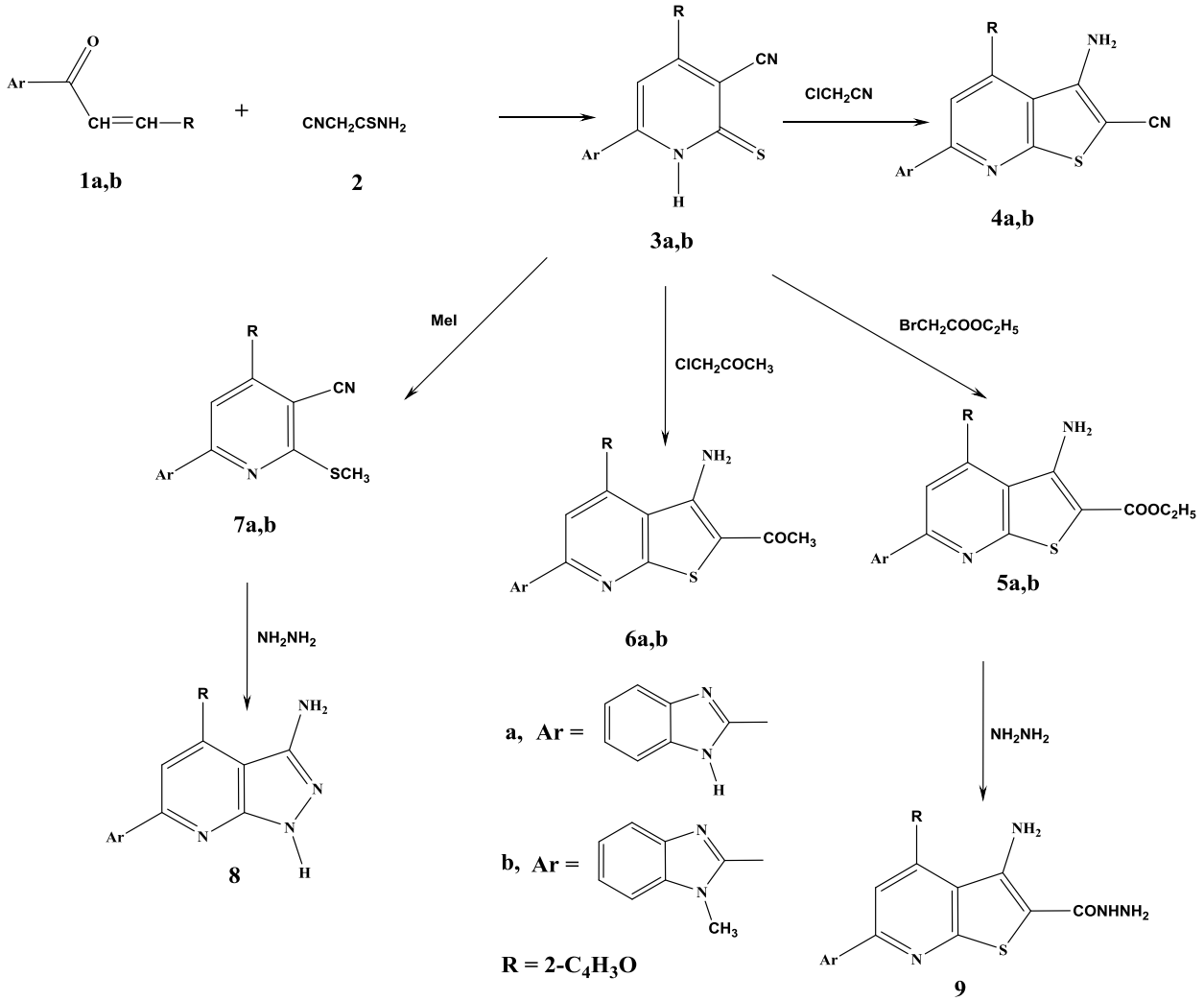
## Results and Discussion:

1-(Aryl)-3-furan-2-yl-propen-1-ones **1a,b** reacted with 2-cyanothioacetamide **(2)** in sodium ethoxide solution under reflux to afford the corresponding pyridinethione derivatives **3a,b**, respectively, (Scheme 1). IR ($\upsilon$ $cm^{-1}$) spectra of **3a** and **3b** showed absorption bands at 3367, 3109 for (NH) and ~ 2210 for (CN) groups. The mass spectra of **3a** and **3b** gave molecular ion peaks at *m/z* = 316 and *m/z* = 332 respectively, corresponding to the assigned structures. Structures of compounds **3a,b** were supported by their elemental analyses and $^1$HNMR spectra. The synthetic potentiality of compounds **3a,b** were investigated through their electophilic substitution reactions with several alkylating agents. Thus, compounds **3a,b** reacted with each of chloroacetonitrile, ethyl bromoacetate and chloroacetone to give products **4a,b-6a,b** respectively. IR ($cm^{-1}$) spectrum of compound **4a** showed absorption bands at 3472, 3351, 3232 for $NH_2$ and NH groups and an absorption band for cyano group at 2193. Also, $^1$H NMR

(δ ppm) spectrum of **5a** revealed signals at 1.44(t, 3H, $CH_3$), 4.42 (q, 2H, $CH_2$), 6.70 (s, 1H, 5-H of the pyridinethione ring), 7.27-8.76 (m, 7H, ArH), 9.50 (s, 1H, NH), 11.56 (b, 2H, $NH_2$) and no signals for -$CH_2$- protons were detected. The Mass spectrum of **6a** showed parent peak at *m/z* = 374 which corresponds to the molecular formula. Similarly, compounds **4b-6b** structures were confirmed by elemental analyses and spectral data.

Compounds **3a,b** reacted with iodomethane to give the corresponding methyl sulfide derivatives **7a,b** respectively (Scheme 1), as evident from their elemental analyses and spectral data. Their IR ($cm^{-1}$) spectrum showed absorption bands at 2211 $cm^{-1}$ for CN group and $^1$H NMR spectrum for compound **7b** revealed the signals at δ 4.19 (s, 6H, $2CH_3$), 6.53 (s, 1H , 5-H of the pyridinethione ring), 7.20-8.57 (m, 7H, Ar`H). Also, structure of compound **7a** was confirmed by its mass spectrum which showed parent peak at *m/z* = 332. Compound **7a** reacted with hydrazine hydrate to give product **8** in a moderate yield (Scheme 1). IR ($cm^{-1}$) spectrum of compound **8** revealed absorption bands at 3435, 3278, 3166 for the amino group and NH group, and no absorption was detected for the cyano group. Also, its mass spectrum showed a peak corresponding to the molecular ion at *m/z* 316.

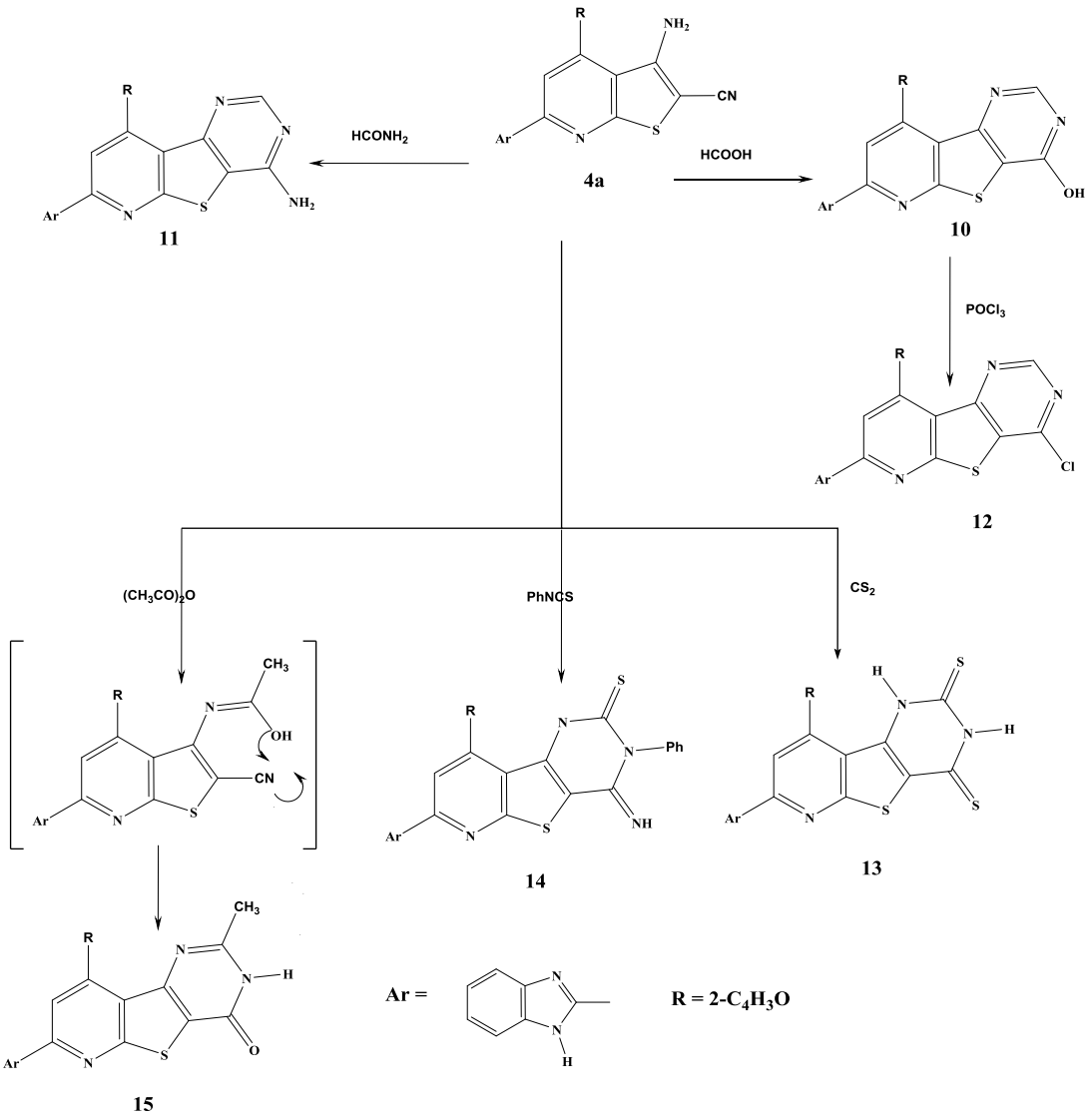
Moreover, 3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid methyl ester **(5a)** reacted with hydrazine hydrate in absolute ethanol to give the corresponding derivative **9**. The IR ($cm^{-1}$) spectrum of **9** showed no absorption band for carbonyl (ester group), while showed absorption band for newly formed $NHNH_2$ group at 3294, 3209, 3109.




**Scheme 1**

Also, compound **4a** as a typical enaminonitrile derivative was reacted with formic acid to afford 7-(1H-benzoimidazl-2-yl)-9-furan-2-yl-pyrido-[3',2':4,5]thieno[3,2-d]-pyrimidin-4-ol **(10)**, (Scheme 2). The IR ($cm^{-1}$) spectrum of this reaction product showed no absorption band for the cyano group and the appearance of the absorption bands for OH and NH groups at 3420 and 3138. Its mass spectrum showed peak at *m/z* 385 (M+). Both IR ($cm^{-1}$) and mass spectra confirmed the proposed structure **10.**

Similarly, compound **4a** reacted with $HCONH_2$ in HCOOH to give compound **11** (Scheme 2). The IR ($cm^{-1}$) spectrum of the product showed no absorption band for cyano group and revealed the appearance of the absorption bands for $NH_2$, NH groups at 3309, 3146, 3109 $cm^{-1}$. The mass spectrum of this product showed a peak at *m/z* 384 which confirmed structure **11**. Compound **10** reacted with $POCl_3$ to give 7-(1H-benzoimidazol-2-yl)-4-chloro-9-furan-2-yl-pyrido[3',2':4,5]thieno[3,2-d] pyrimidine **(12)** in good yield. Its mass spectrum showed a peak at *m/z* 404 corresponding to its molecular weight which confirmed structure **12**.

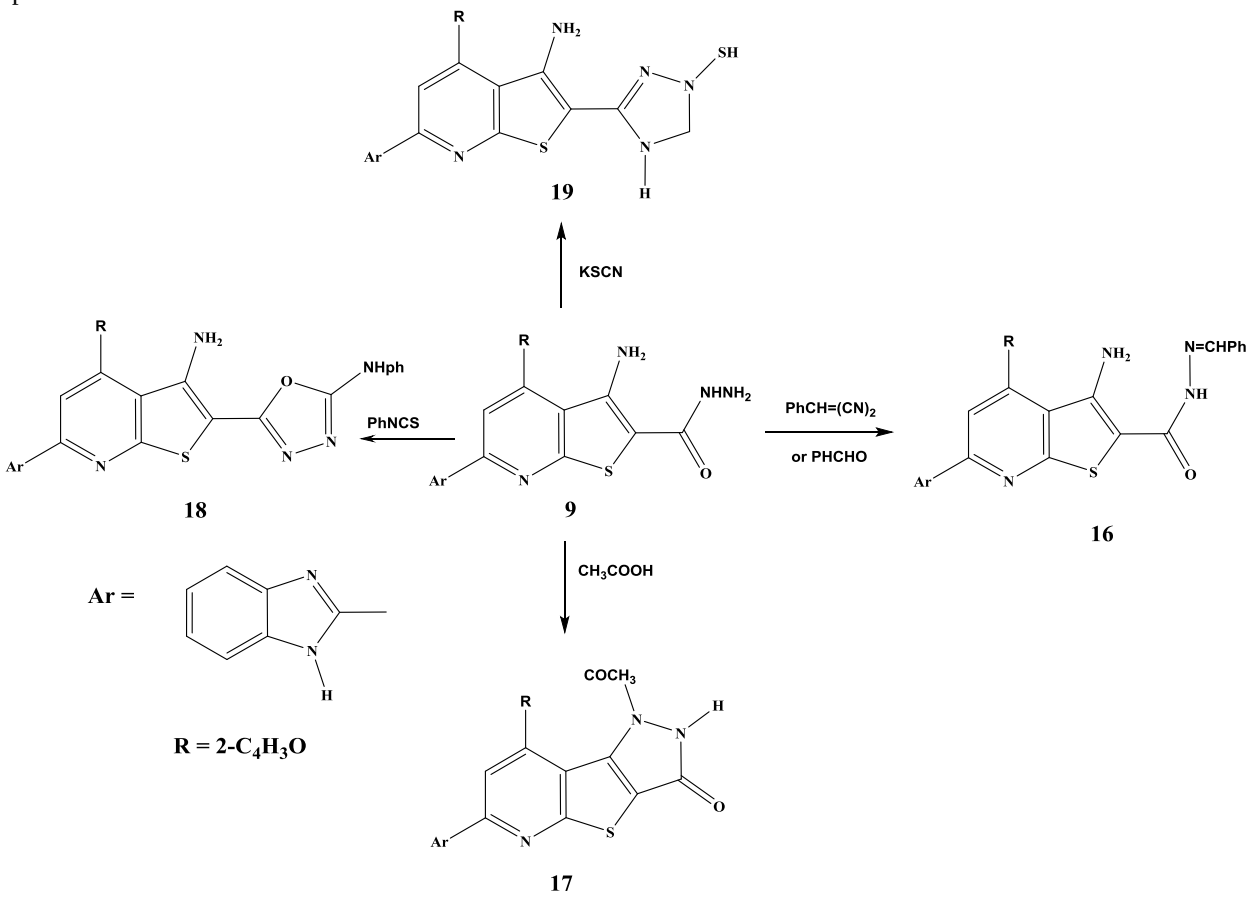



**Scheme 2**

On the other hand, compound **4a** reacted with each of carbon disulfide and phenyl isothiocyanate to give compounds **13** and **14** respectively. Structures **13** and **14** were elucidated on the basis of their elemental analyses and spectral data. The IR ($cm^{-1}$) spectrum of compound **13** showed no absorption band for cyano group and revealed the appearance of the absorption bands for NH groups at 3446, 3236 and 3113 $cm^{-1}$. The mass spectrum of this product showed a peak at *m/z* 433 which confirmed the corresponding structure **13**, (scheme 2).

Also, compound **4**a reacted with acetic anhydride to give 7-(1H-benzoimidazol-2-yl)-9-furan-2-yl-2-methyl-3H-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidin-4-one (**15**). The IR ($cm^{-1}$) spectrum of this reaction product showed no absorption band for cyano group and revealed the appearance of the absorption bands for NH groups at 3375, 3116 and the carbonyl group CO at 1662. The $^1H$ NMR spectrum of this product showed signals at δ 2.89 **(**s, 3H, $CH_3$), δ 6.82 (s, 1H, 5-H of thienopyridine ring), δ 7.26-8.87 (m, 7H, Ar' H), 12.94 (s, 1H, NH) and 13.33 (s, 1H, NH).

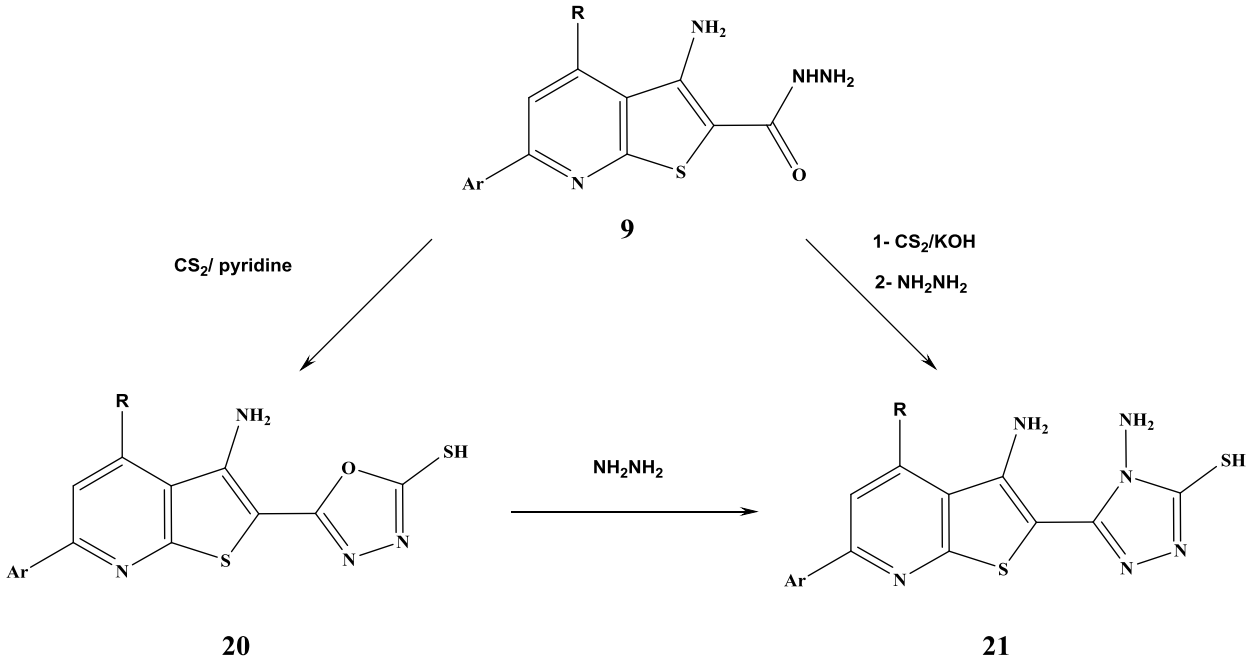
Compound **9** reacted with cinnamonitrile derivative to afford compound **16**. The IR ($cm^{-1}$) spectrum of **16** showed absorption bands of NH and $NH_2$ at 3464, 3307, 3244, 3109 and hydrazidic carbonyl at 1643. Its mass spectrum showed parent peak at *m/z* 478. The reaction seemed to proceed via an ylidene exchange with the elimination of one molecule of malononitrile. This mechanism was confirmed by the preparation of **16** through the reaction of **9** with benzaldehyde (scheme 3) and was found to be identical in all aspects with the sample obtained from the previous route (m.p., mixed m.p., TLC). Also, 1-acetyl-6-(1H-benzoimidazol-2-yl)-8-furan-2-yl-1,2-dihydro-pyrazolo[3`,4`:4,5]thieno[2,3-b]pyrimidin-3-one derivative **(17)** was formed *via* treatment of **9** with glacial acetic acid (scheme 3), the structure of the latter compound was elucidated based on the elemental analysis and spectral data.




**Scheme 3**

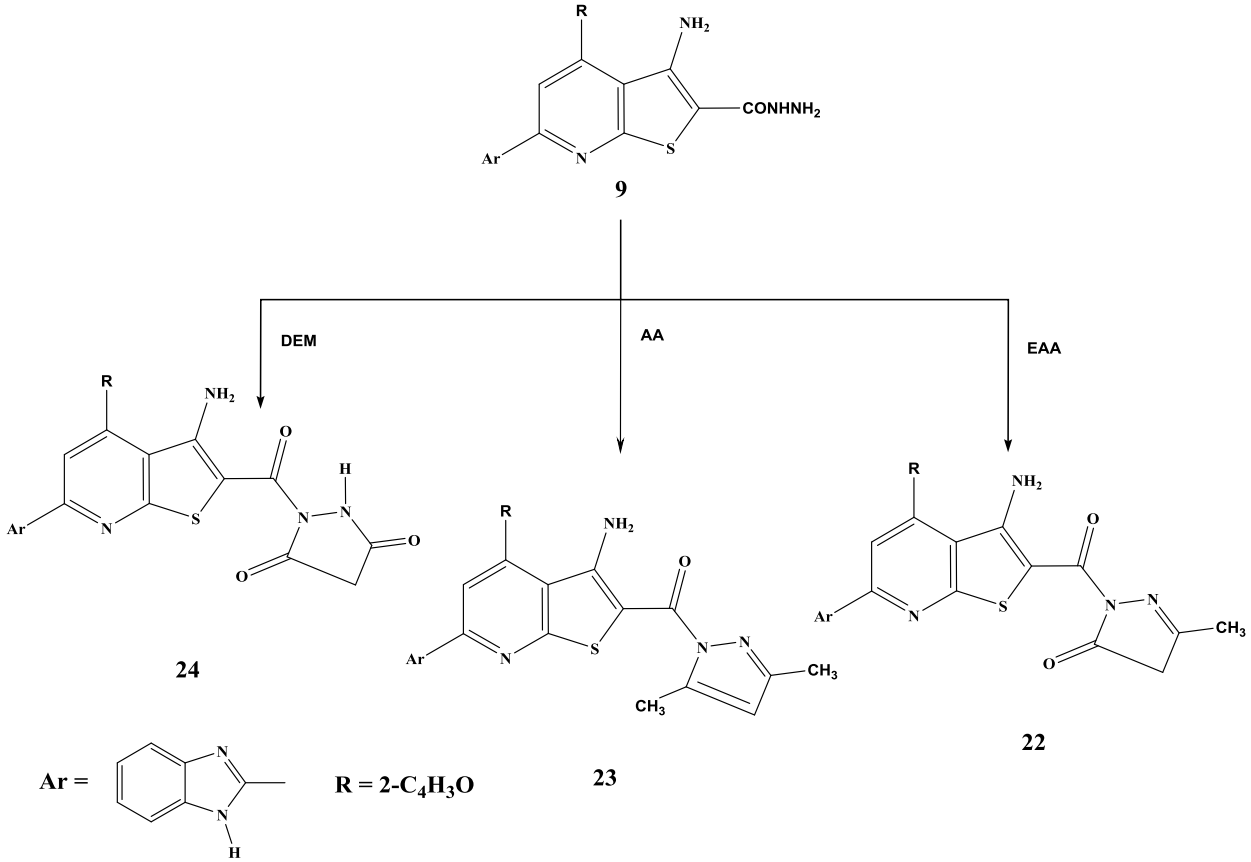
Compound **9** reacted with sulfur containing compounds, such as phenyl isothiocyanate, carbon disulphide and potassium thiocyanate to synthesize different heterocyclic derivatives **18, 19** and **20**, respectively. Thus, compound **9** reacted with phenyl isothiocyanate to give the corresponding derivative **18**, (Scheme 3). Structure of **18** was elucidated based on elemental analysis and spectral data. On the other hand, compound **9** reacted with potassium thiocyanate to give the corresponding derivative 5-[3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl]-4H-[1,2,4]triazole-3-thiol **(19)** (scheme 3). The structure of the latter compound was elucidated based on the elemental analysis and spectral data.

Compound **9** reacted also, with carbon disulphide in pyridine to give the corresponding 5-[3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl]-[1,3,4]oxadiazole-2-thiol derivative (**20)** (Scheme 4). The IR spectrum of **20** showed absorption bands at 3483, 3331, 3220, 2923 $cm^{-1}$ for $NH_2$, NH and SH groups. The mass spectrum of **20** showed parent peak at *m/z* 432 which confirmed structure **20**. Meanwhile, when compound **9** was refluxed with carbon disulfide in ethanolic potassium hydroxide solution followed by reaction with hydrazine hydrate to afforded the corresponding triazole derivative **21** (Scheme 4). The IR spectrum of **21** showed absorption bands of $NH_2$, NH and SH 3444, 3307, 3244, 3109, 2926 $cm^{-1}$. The mass spectrum of **21** showed peak at *m/z* 446 which confirmed the corresponding structure **21**. Structure **21** was confirmed by its alternative preparation by the reaction of **20** with hydrazine hydrate (Scheme 4) and was found to give a sample identical in all aspects with the one obtained from the previous reaction (m.p., mixed m.p., TLC).




**Scheme 4**

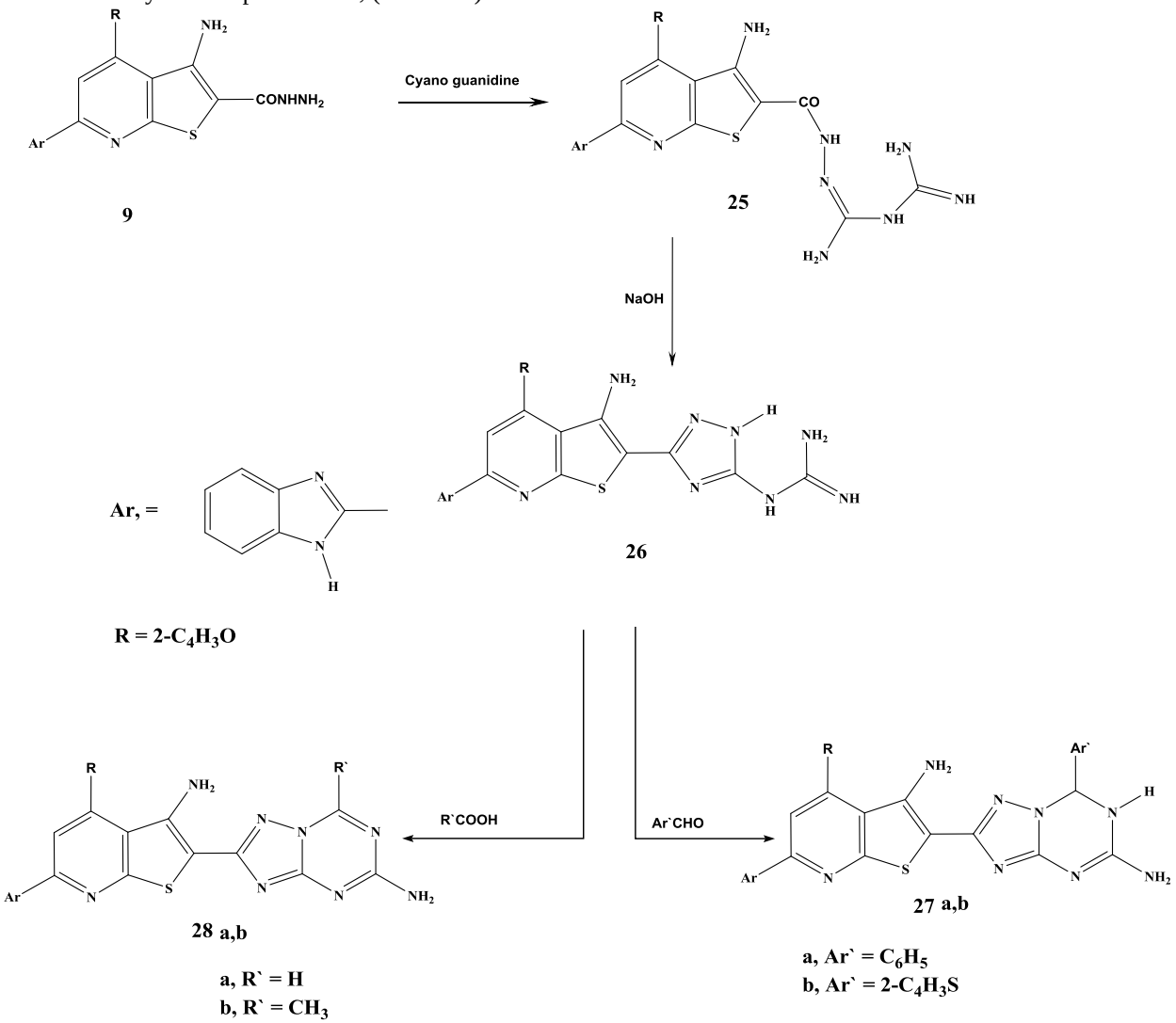
Meanwhile, compound **9** reacted with different β-dicarbonyl compounds such as ethyl acetoacetate, acetylacetone and diethyl malonate to afford 2-pyrazol-2-yl-thieno[2,3-b]pyridine derivatives **22**, **23** and **24**, respectively (scheme 5). Structures of compounds **22-24** were confirmed based on their elemental analyses and spectral data, *cf.* experimental section.




**Scheme 5**

Compound **9** reacted also with cyanoguanidine to give compound **25** (scheme 6). The IR ($cm^{-1}$) spectrum of this reaction product showed no absorption band for cyano group and revealed the appearance of the absorption bands for $NH_2$ and NH groups at 3453, 3338, 3318 and for the carbonyl group at 1650. The mass spectrum of this product showed a peak at *m/z* 474 which confirmed the corresponding structure **25**. Compound **25** reacted with sodium hydroxide solution to give the corresponding derivative **26** (scheme 6). The structure of the latter compound was elucidated based on the elemental analysis and spectral data.

Finally, compound **26** reacted with aromatic aldehydes and aliphatic acids to give the corresponding derivatives **27a,b** and **28a,b** respectively (scheme 6). The IR ($cm^{-1}$) spectrum of **27a** showed no absorption band for the carbonyl group (CO) and revealed absorption bands for $NH_2$ and NH groups at 3453, 3338, 3318. The mass spectrum of this product showed peak at *m/z* 544 which confirmed the corresponding structure **27a**. Also, the IR ($cm^{-1}$) spectrum of **28a** showed no absorption band for the carbonyl group (CO) and revealed absorption bands for $NH_2$ and NH groups at 3426, 3340, 3320. The mass spectrum of this product showed peak at *m/z* 466 which confirmed the corresponding structure **28a.** Similarly, structures **27b** and **28b** were elucidated based on the elemental analysis and spectral data, (scheme 6).




**Scheme 6**

**Antimicrobial Activity**

The antibacterial and antifungal activities were carried out at the Microbiology Division of the Microanalytical Center at Cairo University, using the diffusion plate method. A bottomless cylinder containing a measured quantity (1 mL, 20 mg/mL) of the sample is placed on a plate (7 cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium) which has been heavily seeded with the spore suspension of the test

organism. After incubation (24 hrs for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter x 100). All measurements were done in DMSO as a solvent which has zero inhibition activity. The obtained results were compared with some reference antibiotics that were purchased from Egyptian markets. Surprisingly, all the tested compounds were found to exhibit no activity against both *Escherichia coli* and *Staphylococcus aureus* microorganisms with respect to the used reference and also no activity against *Aspergillus Flavus* fungus which was not expected for these moieties prepared in our previous work[29,30].

**Experimental:**

All melting points were measured on an Electrothermal melting point apparatus and are uncorrected.IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The HNMR spectra were recorded on Varian Mercury at 300 MHz spectrometer using TMS as internal standard and DMSO-d6 as solvent and chemical shift are expressed as δ ppm units. Mass spectra were recorded on GCMS-QP 1000 EX spectrometer using inlet type at the at 70 ev. Elemental analyses were carried out at the Microanalytical center of Cairo University.

**Synthesis of 3a,b**

A mixture of each of 1-(1H-benzimdizol-2-yl)-3-Furan-2-ylpropenone **2a** (19 g, 80 mmoles), 3-Furan-2-yl-)-1-(1-methyl-1H-benzimdizol-2-yl)propenone **2b** (80 mmoles) and 2-cyanothioacetamide (80 mmoles) in 50 ml sodium ethoxide solution (1.84 g of Na in 50 ml ethanol) was heated under reflux for 4-6 hours. The reaction mixture was cooled, the so formed precipitates was filtered off and washed with cooled diluted methanol, dried and recrystallized from the proper solvent.

**6-(1H-Benzimdizol-2-yl)-4-furan-2-yl-2thioxo--1,2-dihydr-pyridine-3-carbonitrile (3a)**: Deep yellow crystals (98%) from ethanol; m.p. > 300$^{o}$C; IR ( υ cm$^{-1}$): 2210 (CN), 3367 (b, 2NH); MS (m/z) = 318; $^{1}$HNMR (DMSO-d6) (δ ppm): 6.74 (s ,1H, 5-H of pyridinethione ), 7.21–8.00 (m, 7H, Ar`H), 11.93 (b, 2H, 2NH). Anal. for $C_{17}H_{10}N_4OS$ (318.86), Calcd/Found (%): C (64.14/63.97), H (3.17/3.00), N (17.60/17.59), S (10.07/10.00).

**4-(furan-2-yl)- 6-(1-methyl-1H- benzimdizol-2-yl)-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (3b):** Brown crystals (60%) from DMF; m.p. = 235$^{o}$C; IR (υ cm$^{-1}$): 2210 (CN), 3109 (NH); MS (m/z) = 332; $^{1}$HNMR (DMSO-d6) (δ ppm): 3.87 (s, 3H, $CH_3$ ), 6.69 (s, 1H, 5-H of pyridinethione), 7.26-8.49 (m, 7H, Ar`H), 10.20 (s, 1H, NH). Anal. for $C_{18}H_{12}N_4OS$ (332.39), Calcd/Found(%): C (65.04/65.00), H (3.64/3.60), N (16.86/16.70), S (9.65/9.50).

**Synthesis of 4a,b, 5a,b ,6a,b and 7a,b (General procedure):**

A mixture of **3a (3b)** (10 mmoles) and potassium hydroxide (0.56g, 10 mmoles) in N,N–dimethylformamide (10ml) was stirred for 2 hrs at room temperature. Each of chloroacetonitrile, ethyl bromoactate, chloroactone and methyl iodide (10 mmoles each) was added and stirring was continued for 2 hrs. The so formed precipitate were collected by filtration, washed with ethanol, dried and recrystallized from the proper solvent.

**3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carbonitrile (4a):** Green crystals (85%) from DMF; m.p. >300$^{o}$C; IR (υ cm$^{-1}$): 2193 (CN), 3472, 3351, 3232 ( $NH_2$, NH) ; $^{1}$HNMR (DMSO-d6) (δ ppm):6.10 (s, 1H, 5-H of pyridinethione), 7.36 -8.49 (m, 7H, Ar` H), 9.41(s, 1H, NH), 10.45 (b, 2H, $NH_2$). Anal. for $C_{19}H_{11}N_5OS$ (357.40), Calcd/Found(%): C (63.85/63.89), H (3.10/3.00), N (19.60/19.60), S (8.97/8.98).

**3-Amino-4-furan-2-yl-6-(1-methyl-1H-benzoimidazol-2-yl)-thieno[2,3-b]pyridine-2-carbonitrile (4b):** Brown crystals (27%) crystallized from DMF; m.p. >300$^{o}$C; IR (υ cm$^{-1}$): 2200 (CN); 3439, 3351, ($NH_2$,); $^{1}$HNMR (DMSO-d6) (δ ppm): 2.88 (s, 3H, $CH_3$), 6.58 (s, 1H, 5-H of the pyridinethione), 7.30-8.38 (m, 7H, Ar`H); Anal. for $C_{20}H_{13}N_5OS$ (371.42), Calcd/Found(%): C (64.68/64.68), H (3.53/3.50), N(18.86/), S(8.63/8.50).

**3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid methyl ester (5a):** Orange crystals, crystallized from ethanol/DMF (90%); m.p.= 220$^{o}$C; IR (υ cm$^{-1}$): 1752 (CO ester); 3484, 3351, 3086 ($NH_2$, NH); $^{1}$HNMR (DMSO-d6) (δ ppm): 1.44 (t, 3H, $CH_3$), 4.42 (q, 2H, $CH_2$), 6.70 (s, 1H, 5-H of the pyridinethione ring),7.27-8.76 (m, 7H, Ar`H), 9.50 (s, 1H, NH), 11.56 (b, 2H, $NH_2$). Anal. for $C_{21}H_{16}N_4O_3S$ (404.45), Calcd/Found(%): C (63.36/63.40), H (3.99/4.00), N (13.85/13.90), S (7.93/8.00).

**3-Amino-4-furan-2-yl-6-(1-methyl-1H-benzoimidazol-2-yl)-thieno[2,3-b]pyridine-2-carboxylic acid methyl ester (5b):** Orange crystals, crystallized from ethanol/DMF (20%); m.p.= 180$^{o}$C; IR (υ cm$^{-1}$): 1735 (CO ester); 3429, 3109 ($NH_2$,); $^{1}$HNMR (DMSO-d6) (δ ppm): 1.24 (t, 3H, $CH_3$), 4.20 (s, 3H, $CH_3$), 4.00 (q, 2H, $CH_2$), 6.50 (s, 1H, 5-H of the pyridinethione), 7.18-7.94 (m,7H,Ar`H), 10.90 (b, 2H, $NH_2$). Anal. for $C_{22}H_{18}N_4O_3S$ (418.48), Calcd/Found(%): C (63.14/63.00), H (4.34/4.20), N (13.39/13.30), S (7.66/7.50).

**1-[3-Amino-6-(1H-benzimodazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl-ethanone (6a):** white crystals; crystallized from ethanol/DMF (39%) ; m.p >300$^{o}$C; IR (υ cm$^{-1}$): 1734 (CO), 3456, 3296 ($NH_2$); MS (m/z) = 374; $^{1}$HNMR (DMSO-d6)(δ ppm): 2.43 (s, 3H, $CH_3$), 6.83 (s,1H, 5-H of pyridinethione), 7.24-8.40(m, 7H, Ar`H), 13. 33 (b, 2H, $NH_2$). Anal for $C_{20}H_{14}N_4O_2S$ (374.42), Calcd/Found(%): C (64.16/64.00), H (3.77/3.70), N (14.96/15.00), S (8.56/8.50).

**1-[3-Amino-4-furan-2-yl-6-(1-methyl-1H-benzimodazol-2-yl)-thieno[2,3-b]pyridine-2-yl-ethanone (6b):** Green crystals; crystallized from DMF (25%); m.p. >300$^{o}$C; IR (υ cm$^{-1}$): 1711 (CO), 3423, 3054 ($NH_2$); MS (m/z) = 374(M+); $^{1}$HNMR (DMSO-d6) (δ ppm): 3.33 (s, 6H, $2CH_3$), 6.71 (s,1H, 5-H of pyridinethione), 7.25-8.42 (m, 7H, Ar`H),10. 98 (b, 2H, $NH_2$). Anal for $C_{21}H_{16}N_4O_2S$ (388.45), Calcd/Found(%): C (64.93/65.00), H (4.15/4.00), N (14.42/14.40), S (8.25/8.30).

**6-(1H-Benzoimidazol-2-yl)-4-furan-2-yl-2-methylsulfanyl-nicotinonitrile (7a):** White crystals ; from ethanol (75%); m.p. = 245$^{o}$C; IR (υ cm$^{-1}$): 2211(CN), 3426 (NH); MS (m/z) =332; $^{1}$HNMR (DMSO-d6)(δ ppm): 2.7 (s, 3H, $CH_3$),6.81 (s,1H ,5-H of the pyridinethione), 7.2-8.06 (m, 7H, Ar` H), 9.87 (s, 1H, NH). Anal. for $C_{18}H_{12}N_4OS$ (332.39), Calcd/Found(%): C (65.04/65.00), H (3.64/3.60), N (16.86/16.86), S (9.65/9.70).

**4-Furan-2-yl-6-(1-methyl-1H-Benzoimidazol-2-yl)2-methylsulfanyl-nicotinonitrile (7b):** White crystals; from ethanol (30%); m.p. = 250$^{o}$C ; IR (υ cm$^{-1}$): 2229 (CN); $^{1}$HNMR ($CHCl_3$)(δ ppm): 4.19 (s, 6H, $2CH_3$), 6.53 (s,1H ,5-H of the pyridinethione), 7.20-8.57 (m, 7H, Ar` H) Anal. For $C_{19}H_{14}N_4OS$ (346.41), Calcd/Found(%): C (65.88/65.90), H (4.05/4.90), N(16.17/16.16), S (9.26/9.20).

**Synthesis of 6-(1H-Benzimidazol-2-yl)-4-furan-2-yl-1H-pyrazolo[3,4-b]pyridin-3-ylamine (8):**
A mixture of **7a** (5mmoles) and excess of hydrazine hydrate was heated under reflux for 48hrs. The reaction mixture was cooled; the so formed precipitates was collected by filtration, washed with cold ethanol, then dried and recrystallized from DMF. Yellow crystals (40%); m.p. > 300$^{o}$C; IR (υ cm$^{-1}$): 3435, 3278, 3166 ($NH_2$, NH); MS (m/z) = 316(M+). Anal for $C_{17}H_{12}N_6O$ (316.32), Calcd/Found (%): C (64.55/64.60), H (3.82/3.90), N (26.57/26.80).

**Synthesis of 3-Amino-6-(1H-benzimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carboxylic acid hydrazide (9):**
A mixture of **(5a)** (5mmoles) and excess of hydrazine hydrate in absolute ethanol (20 ml) was heated under reflux for 36 hrs. The reaction mixture was cooled; the so formed precipitate was collected by filtration, dried and recrystallized from ethanol/DMF. Yellow crystals (54%); m.p. = 285$^{o}$C; IR (υ cm$^{-1}$): 1662 (CO), 3294, 3209, 3109 ($NH_2$, NH); MS(m/z) = 390(M+). Anal. for $C_{19}H_{14}N_6O_2S$ (390.43); Calcd/Found(%): C (58.45/58.56), H (3.61/3.59), N (21.53/21.50), S (8.21/8.20).

**Synthesis of7-(1H-bezimidazol2-yl)-9-furan-2-yl-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidin-4-ol (10):**
A mixture of **(4a)** (10 mmoles) and formic acid (20 ml) was heated under reflux for 7 hrs.The reaction mixture was cooled; the so formed precipitate was collected by filtration, dried and recrystallized from DMF.Green crystals (38%); m.p. >300$^{o}$C; IR (υ cm$^{-1}$): 3420 (OH), 3138 (NH); MS(m/z) = 385(M+). Anal. for $C_{20}H_{11}N_5O_2S$ (385.41), Calcd/Found(%): C (63.33/63.20), H (2.88/3.00), N (18.17/18.15), S (8.32/8.29).

**Synthesis of 7-(1H-Benzimidazol-2-yl)-9-furan-2-yl-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidin-4-yl amine (11):**
A mixture of **4a** (5mmoles), formamide (20ml) was heated under reflux for 12 hours. The reaction mixture was cooled, the so formed precipitate was collected by filtration, dried and recrystallized from DMF. Black crystals (90%); m.p. = 170$^{o}$C; IR (υ cm$^{-1}$): 3309, 3146, 3109 ($NH_2$, NH); MS (m/z) = 384(M+). Anal. for $C_{20}$ $H_{12}N_6OS$ (384.42), Calcd. /Found(%) C (62.49/62.50), H (3.15/3.10), N (21.86/21.90), S (8.34/8.35).

**Synthesis of 7-(1H-Benzimidazol-2-yl)-4-chloro-9-furan-2-yl-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidine (12):**

Compound **10** (3mmoles) was heated with $POCl_3$ (15ml) under reflux for 7 hrs. The reaction mixture was cooled; the so formed precipitate was collected by filtration, washed with cold ethanol, dried and recrystallized from DMF. Black crystals (84.4%); m.p. = 290$^oC$; IR (υ $cm^{-1}$): 3417 (NH); MS (m/z) = 404(M+). Anal. for $C_{20}$ $H_{10}ClN_5$ OS (403.85); Calcd/Found(%): C (59.48/ 59.50), H (2.50/2.70), N (17.34/17.50), S (7.94/7.98).

**Synthesis of 7-(1H-Benzimidazol-2-yl)-9-furan-2-yl-1H-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidin-2,4-dithione (13)**:
A mixture of **4a** (2mmoles) and carbon disulphide (5 ml) in pyridine (15 ml) was heated under reflux for 7 hours. The reaction was cooled, the so formed precipitate was filtered off, dried and recrystallized from ethanol/DMF. Yellowish brown crystals (44%); m.p. = 285$^oC$; IR (υ $cm^{-1}$): 3470, 3346, 3113 (3NH); MS(m/z) = 433(M+). Anal. for $C_{20}H_{11}N_5OS_3$ (433.54); Calcd/Found(%): C (55.41/55.51), H (2.56/2.60), N (16.15/16.13), S (22.19/22.20).

**Synthesis of7-(1H-Bezimidazol-2-yl)-9-furan-2-yl-4-imino-3-phenyl-3,4-dihydro-1H-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidin-2-thione(14)**:
A mixture of **4a** (1mmole) and phenyl isothiocyanate (1mmole) in pyridine (10 ml) was heated under reflux for 7 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, dried and recrystallized from ethanol/DMF. Yellowish brown (40%); m.p.= 260$^oC$; IR (υ $cm^{-1}$): 3467, 3348 (2NH); MS(m/z) = 492(M+). Anal. for $C_{26}H_{16}N_6OS_2$ (492.59), C (63.40/63.50), H (3.27/3.30), N (17.06/17.00), S (13.02/13.00).

**Synthesis of 7-(1H-Bezimidazol-2-yl)-9-furan-2-yl-2-methyl-3H-pyrido[3`,2: 4,5]thieno[3,2-d]pyrimidin-4-one (15):**
A mixture of **4a** (2mmole) and acetic anhydride (20ml) was heated under reflux for 7hours. The so formed precipitate was filtered off, dried and recrystallized from DMF. Yellow crystals (70%) m.p. > 300$^oC$; IR (υ $cm^{-1}$): 1662 (CO), 3375, 3116 (2NH); $^1$HNMR (DMSO-d6) (δ ppm): 2.89 (s, 3H, $CH_3$), 6.84 (s, 1H, 5-H of the pyridinethione), 7.26-8.87 (m, 7H, Ar`H), 12.94 (s, 1H, NH), 13.33(s, 1H, NH). Anal. for $C_{21}H_{13}N_5O_2S$ (399.43), Calcd/Found(%): C (63.15/63.15), H (3.28/3.50), N (17.53/ 17.33), S (8.03/8.00).

**Synthesis of N`-(4-Benzylidene)-3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carbohydrazide derivative** (**16)**:
A mixture of **9** (2.5 mmoles) and benzylidene malonitrile (2.5 mmoles) and/or benzaldhyde (2.5 mmoles) in pyridine (10 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, washed with ethanol, dried and recrystallized from DMF. Red crystals (90%); m.p. = 243$^oC$; IR (υ $cm^{-1}$): 1662 (CO), 3464, 3307 ($NH_2$), 3109, 3043 (2NH), MS(m/z) = 478(M+). Anal. for $C_{26}H_{18}N_6O_2S$ (478.54), Calcd/Found(%): C (65.26/65.30), H (3.79/400), N (17.56/17.70), S (6.70/6.85).

**Synthesis of 1-Acetyl-6-(1H-benzimidazol-2-yl)-8-furan-2-yl-1,2-dihydro-pyrazolo[3`,2`:4,5]thieno[2,3-b]pyridin-3-one (17):**
A mixture of **9** (2 mmoles) in acetic acid (15 ml) was heated under reflux for 5 hours. The excess solvent was evaporated, the so formed precipitate was filtered off and washed with ethanol, dried and recrystallized from DMF. Orange crystals; (82%); m.p. >300$^oC$ IR (υ $cm^{-1}$): 1671 (CO), 3492, 3349 (2NH), MS (m/z) = 415(M+); $^1$HNMR (DMSO-d6) (δ ppm): 2.03 (s, 3H, $CH_3$), 6.09 (s, 1H, 5-H of the pyridinethione), 6.74-8.45 (m, 7H, Ar`H), 10.35 (s, 1H, NH), 13.37 (s, 1H, NH). Anal. for $C_{21}H_{13}N_5O_3S$ (415.43), Calcd/Found (%): C (60.72/60.80), H (3.15/3.17), N (16.86/16.90), S (7.72/7.75).

**Synthesis of 6-(1H-Benzoimidazol-2-yl)-4-furan-2-yl-2-(5-phenyl-[1,3,4]oxadiazol-2-yl)thieno[2,3-b]pyridine-3-ylamine (18):**
A mixture of (2.5mmoles) and phenyl isothiocyanate (2.5 mmoles) in pyridine was heated under reflux for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, dried and recrystallized from ethanol/DMF. Reddish brown crystals (25%); m.p. = 215-217$^oC$; IR (υ $cm^{-1}$): 3469, 3325, 3109 ($NH_2$, 2NH); MS (m/z) = 491(M+). Anal. for $C_{26}H_{17}N_7O_2S$ (491.54), Calcd/Found(%) C (63.53/63.50), H (3.49/3.50), N (19.95/20.00), S (6.52/6.50).

**Synthesis of 5-[3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl]-4H-[1,2,4]triazol-3-thiol (19):**
A mixture of **9** (2.5 mmoles), potassium thiocyanate (2.5 mmoles) and HCl (6ml) in ethanol (10 ml) was heated under reflux for 4 hours. The reaction mixture was cooled, the so formed precipitate was filtered and dissolved in 10

ml of 10 % KOH solution which in turn refluxed for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered, dried and recrystallized from ethanol/DMF. Brown crystals (50%); m.p. > 300$^{o}$C; IR (υ cm$^{-1}$), 3466, 3348, 3205, 3109, 2924 ($NH_2$, 2NH, SH); MS (m/z) = 431(M+). Anal. for $C_{20}H_{13}N_7OS_2$ (431.50), Calc/Found(%): C (55.67/55.70), H (3.04/3.00) , N (22.70/22.80), S (14.86/14.90) .

**Synthesis of 5-[3-Amino-6(1H-benzimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl][1,3,4] oxodiazole-2-thiol (20):**

A mixture of **9** (2.5mmoles), and carbon disulphide (5ml) in pyridine (15 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, dried and recrystallized from ethanol/DMF. Reddish brown crystals (57%); m.p. = 266$^{o}$C; IR (υ cm$^{-1}$): 3483, 3331, 3220, 2928 ($NH_2$, NH, SH); MS(m/z) = 432(M+). Anal. for $C_{20}H_{12}N_6O_2S_2$ (432.49), Calcd/Found(%): C (55.54/55.50), H (2.80/2.90), N (19.43/14.40), S (14.83/14.90).

**Synthesis of 21**

**Method A**

A mixture of **9** (2.5 mmoles) and carbon disulphide (2.5 mmoles) in ethanol (20 ml) was heated under reflux for 10 hours. The resulting precipitate was filtered off and washed with ethanol to give the corresponding carbodithioic derivative which was reacted with hydrazine hydrate in 40% sodium hydroxide solution under reflux for 12 hours. The reaction mixture was cooled, the solution pH was adjusted to pH = 2 using HCl and the resulting precipitate was collected and recrystallized from ethanol/DMF.

**Method B**

A mixture of **20** and hydrazine hydrate in ethanolic solution (10 ml) was heated under reflux for 10 hours. The resulting precipitate was filtered, dried crystallized from ethanol/DMF to give the corresponding amino triazole derivative.

**4-Amino-5-[3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridin-2-yl]-4H-[1,2,4]triazole-3-thiol(21):** Brown crystals (40%); m.p. > 300$^{o}$C; IR (υ cm$^{-1}$): 3444, 3320, 2926 ($NH_2$, SH); MS (m/z) = 446 (M+). Anal. for $C_{20}H_{14}N_8OS_2$ (446.52), Calcd/Found(%): C (53.80/53.82), H (3.16/3.18), N (25.10/25.00), S (14.36/14.40).

**Synthesis of 2-[3-Amino-6(1H- benzimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carbonyl]-5-methyl-2,4-dihydro-pyrazol-3-one (22):**

A mixture of **9** (2.5 mmoles) and ethyl acetoactate (2.5 mmoles) in acetic acid (10 ml) was heated under reflux for 5 hours. The excess solvent was evaporated, the so formed precipitate was filtered, washed with ethanol, dried and recrystallized from ethanol/DMF. Greenish yellow crystals; (60%); m.p. > 300$^{o}$C; IR (υ cm$^{-1}$): 1670, 1617 (2 CO), 3337, 3145, 3089 ($NH_2$, NH); $^{1}$HNMR (DMSO-d6) (δ ppm): 2.41 (s, 3H, $CH_3$), 6.28 (s, 2H, $CH_2$), 6.89 (s, 1H, 5H thienopyridine), 7.27-8.88 (m, 7H, Ar`H), 10.2 (b, 2H, $NH_2$); Anal. for $C_{23}H_{16}N_6O_3S$ (456.49), Calcd/Found(%): C (60.52/60.60), H (3.53/3.70), N (18.41/18.51), S (7.02/7.00).

**Synthesis of[3-Amino-6-(1H-benzimidazol-2-yl)-4-furan-2-yl-thieno [2,3-b]pyridine-2-yl]-(3,5-dimethyl-pyrazol-1-yl)methanone (23):**

A mixture of **9** (2.5mmoles) and acetylacetone (2.5mmoles) was heated under reflux for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, dried and recrystallized from DMF. Black crystals (37%); m.p. >300$^{o}$C; (υ cm$^{-1}$): 1653 (CO), 3340, 3145, 3109 ($NH_2$, NH), MS (m/z) = 456. Anal. for $C_{24}H_{20}N_6O_2S$ (456.53), Calcd/Found(%): C (63.14/63.15), H (4.42/4.40), N (18.41/18.50), S (7.02/7.00).

**Synthesis of 1[3-Amino-6-(1H-benzimdazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carbonyl )-pyrazolidine-3,5-dione (24):**

A mixture of **9** (2.5 mmoles) and diethyl malonate (2.5 mmoles) in acetic acid (15 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, the so formed precipitate was filtered off, dried and recrystalized from DMF. Brown crystals (61%); m.p. > 300$^{o}$C; IR (υ cm$^{-1}$): 1665, 1605 (CO), 3447, 3307 ($NH_2$), 3195, 3058 (2NH), $^{1}$HNMR (DMSO-d6) (δ ppm): 5.66 (s, 2H, $CH_2$), 6.8(s, 1H , 5-H of pyridinethione), 7.30-8.89 (m, 7H ,Ar` H), 9.89 (s, 1H, NH), 10.42 (b, 2H, $NH_2$). Anal for $C_{22}H_{14}N_6O_4S$ (458.46), Calc/Found (%): C (57.64/57.80), H (3.08/3.10), N (18.33/18.35), S (6.99/7.00).

**Synthesis of N-(Amino-{[3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-carbonyl]-hydrazono}-methyl)-guanidine (25):**

A mixture of **9** (5mmoles) in ethanol (5ml), hydrochloric acid (37%, 1 ml) and cyanoguanidine (5.5 mmoles) was heated under reflux with stirring for 8 hrs. After cooling, the product was filtered, washed with cold ethanol, dried and recrystallized from ethanol / DMF. Red crystals (90%); m.p.= 255$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 1650 (CO), 3453, 3338, 3318 ($NH_2$, NH); MS (m/z) = 474(M+). Anal. for $C_{21}H_{18}N_{10}O_2S$ (474.51), Calc/Found(%): C (53.16/53.20), H (3.82/3.90), N (29.52/29.70), S (6.76/6.80).

**Synthesis of N-{5-[3-amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2yl]2[1,2,4]triazol-3-yl }-guanidine (26):**
A mixture of 25 (5mmoles) was heated at 80$^{o}$C in 10% aqueous sodium hydroxide solution (5 ml) for 6 hours. After cooling, the product was filtered, washed with cold water, dried and recrysallized from ethanol. Brown crystals (35%); m.p. > 300$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 3406, 3340, 3109 ($NH_2$, NH); MS (m/z) = 456 (M+). Anal. for $C_{21}H_{16}N_{10}OS$ (456.49), Calcd/Found(%): C (55.25/52.30), H (3.53/3.50), N (30.68/30.70) , S (7.02/7.00) .

**Synthesis of 27a,b**
A mixture of **26** (2.5mmoles), appropriate aldehyde (2.5mmoles) and catalytic amount of piperidine in ethanolic solution (10 ml) was heated under reflux for 18 hours. After cooling, the product was filtered, washed with cold ethanol, dried and recrysallized from ethanol/DMF .
**2-[3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl]-7-phenyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-ylamine (27a):** Deep green crystals (46%); m.p. > 300$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 3422, 3109, 3058 ($NH_2$, NH); MS (m/z) = 544 (M+). Anal for $C_{28}H_{20}N_{10}OS$ (544.60), Calcd/Found(%): C (61.75/61.83), H (3.70/3.90), N (25.72/25.90), S (5.89/6.00).

**2-[3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridine-2-yl]-7-thiophen-2-yl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-ylamine (27b):** orange crystals (50%); m.p. > 300$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 3422, 3100, 3046 ($NH_2$, NH); MS (m/z) = 550 (M+). Anal for $C_{26}H_{18}N_{10}OS_2$ (550.63), Calcd/Found(%): C (56.72/56.83), H (3.30/3.50), N (25.44/25.50), S (11.65/11.70).

**Synthesis of 28a,b**
A mixture of **26** (2.5mmoles), the appropriate acid (2.5mmoles) and catalytic amount of piperidine in ethanolic solution (10 ml) was heated under reflux for 18 hours. After cooling, the product was filtered, washed with cold ethanol, dried and recrysallized from ethanol/DMF.
**7-[3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridin-2-yl]-2-imino-1,2-dihydro-imidazo[1,2-a][1,3,5]triazine (28a):** Black crystals (40%); m.p. > 300$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 3426, 3109, 3070 ($NH_2$, NH); MS (m/z) = 565 (M+). Anal for $C_{23}H_{15}N_9OS$ (565.50), Calcd/Found(%): C (59.35/59.40), H (3.25/3.00), N (27.08/27.10), S (6.89/6.90).

**7-[3-Amino-6-(1H-benzoimidazol-2-yl)-4-furan-2-yl-thieno[2,3-b]pyridin-2-yl]-2-imino-4-methyl-1,2-dihydro-imidazo[1,2-a] [1,3,5]triazine (28b):** Brown crystals (55%); m.p. =245$^{o}$C; IR ($\upsilon$ cm$^{-1}$): 3433, 3113, 3098 ($NH_2$, NH); MS (m/z) = 479(M+). Anal for $C_{24}H_{17}N_9OS$ (479.51), Calcd/Found(%): C (60.12/60.00), H (3.57/3.54), N (26.29/26.30), S (6.67/6.70).

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