Synthesisof Some Fused Heterocyclic Compounds Based on 1-(1-Benzofuran-2-yl)-3-(furan-2-yl)prop-2-en-1-one

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Abstract: 1-(1-Benzofuran-2-yl)-3-(furan-2-yl)prop-2-en-1-one**(3)**reacted with 2-cyanoethanethioamide **(4)**to afford the corresponding 6-(1-benzofuran-2-yl)-4-(furan-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile**(5)**. The synthetic potentiality of compound **5** was investigated in the present study via its reactions with several active-hydrogen containing compoundsaiming to synthesize each of thieno[2,3-b]pyridine derivatives **8a,b**, **11**, **14a**,**b**, **17**, **20**,**23**; 3-aminothieno[2,3-b]pyridine-2-carbohydrazidederivative **24** which used in turn, to prepare(1*H*-pyrazol-1-yl)carbonyl-thieno[2,3-*b*]pyridin-3-amine **26**,N-phenylmethylenethieno[2,3-b]pyridine-2-carbohydrazide**31**, pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidinone derivatives **33**, **35**, **38a,b** andpyrazolo[3',4':4,5]thieno[2,3-b]pyridine-3-one derivative **40**. The structures of the newly synthesized heterocyclic compounds were elucidated by considering the data of both elemental and spectral data.

Index Terms:2-Cyanoethanethioamide; Pyridothienopyrimidinones;N-phenylmethylenethienopyridin-2-carbohydrazides; 2-Thioxopyridine-3-carbonitrile.

1 INTRODUCTION

Thieno[2,3-b]pyridines are of special importance due to the reported biological activities, such as antimicrobial[1-4], potent antitumor[5], antifungal agents[6]and anti-inflammatory[7] activities. Enaminoester moieties were utilized in synthesis of different heterocyclic systems with pronounced biological and pharmaceutical activities such as thienopyrimidines[8].Additionally, derivatives of thieno-[3,2-d]pyrimidines are of interest as biologically active compounds[9,10].In light of all these considerations and in continuation of our long-term interest in the chemistry of pyridines[11-17] we wish to report herein on the scope of 2-thioxopyridine-3-carbonitrile for their hetero-cyclization with some α-halocarbonyl containing reagents. The work has resulted in the formation of several new functionally substituted pyridines which could also, be annulated into fused heterocyclic ring systems.

2 RESULTS AND DISCUSSION

It has been found that 1-(1-benzofuran-2-yl)ethanone[18]**(1)** reacted with furan-2-carbaldehyde**(2)** in 1:1molar ratio to give the corresponding 1-(1-benzofuran-2-yl)-3-(furan-2-yl)prop-2-en-1-one**(3)**whichreacted under reflux with 2-cyanoethanethioamide **(4)**in absolute ethanol containing a catalytic amount of piperidine to afford a reaction product **5**. Such reaction product was formed via a *Michael addition* of -CH_2- in **4** on-CH=CH- of **3** followed by cyclization via dehydration and dehydrogenation to give **5**. Considering the data of IR, ^{1}H NMR, Mass spectrometry and elemental analyses (cf. Exp. Part) the structure of **5** was investigated. The synthetic potentiality of **5** was investigated through its reaction with several active-halogen containing compounds e.g. chloroacetamide, 2-chloro-N-(4-bromophenyl)acet-amide (**6a,b**). Thus, it has been found that compound **5** reacted with chloroacetamide (**6a**) in 1:1 ratio in methanolic sodium under reflux to afford firstly 2-{6-(1-benzofuran-2-yl)-3-cyano-4-(furan-2- yl)pyridine-2-yl}acetamide **7a**which formed through dehydrochlorination. The IR spectrum of **7a** showedthe presence of absorption bands corresponding to the $CONH_2$ and CNfunctions. Its mass spectrum gave the parent peak at m/z = 375 which corresponding to its molecular weight, the base peak at m/z = 331 which corresponds to the fragment of M^+-$CONH_2$ and peak at m/z = 306 which corresponds to the fragment of M^+-furyl, 2H. The formation of compound **7a** was further elucidated *via* its cyclization in ethanolic potassium hydroxide solution to afford the corresponding thieno[2,3-b]pyridine derivative **8a**. In a similar manner,2-chloro N-(4-bromophenyl)acetamide (**6b**) was reacted with compound **5**to afford the corresponding 2-{6-(1-benzofuran-2-yl)-3-cyano-4-(furan-2-yl)pyridine-2-yl}-N-(4-bromophenyl)aceta-mide **7b** which in turn, cyclized in ethanolic potassium hydroxide solution to afford the corresponding thieno[2,3-b]pyridine derivative **8b**.The ^{1}H NMR spectrum of compound **7b** revealed the signals of CH_2at 4.18 ppm, NH at 10.61ppm in addition to aromatic, furan and pyridine protons and the mass spectrum of **8b**gave the parent peak (M^+) at m/z = 530 as well as the isotope peak (M^++2) at m/z = 532 and peak at m/z = 359 which corresponding to the fragment of M^+-NHC_6H_4-4-Br (cf. Exp. Part).Likewise, it has been found that compound **5** reacted with 1-chloroacetone**(9a)**under the same above mentioned experimental conditions to afford 6-(1-benzofuran-2-yl)-4-(furan-2-yl)-2-[(2-oxoprop-yl)sulfanyl]pyridine-3-carbo-nitrile **(10a)**. The IR (cm^{-1}) of this compound showed the

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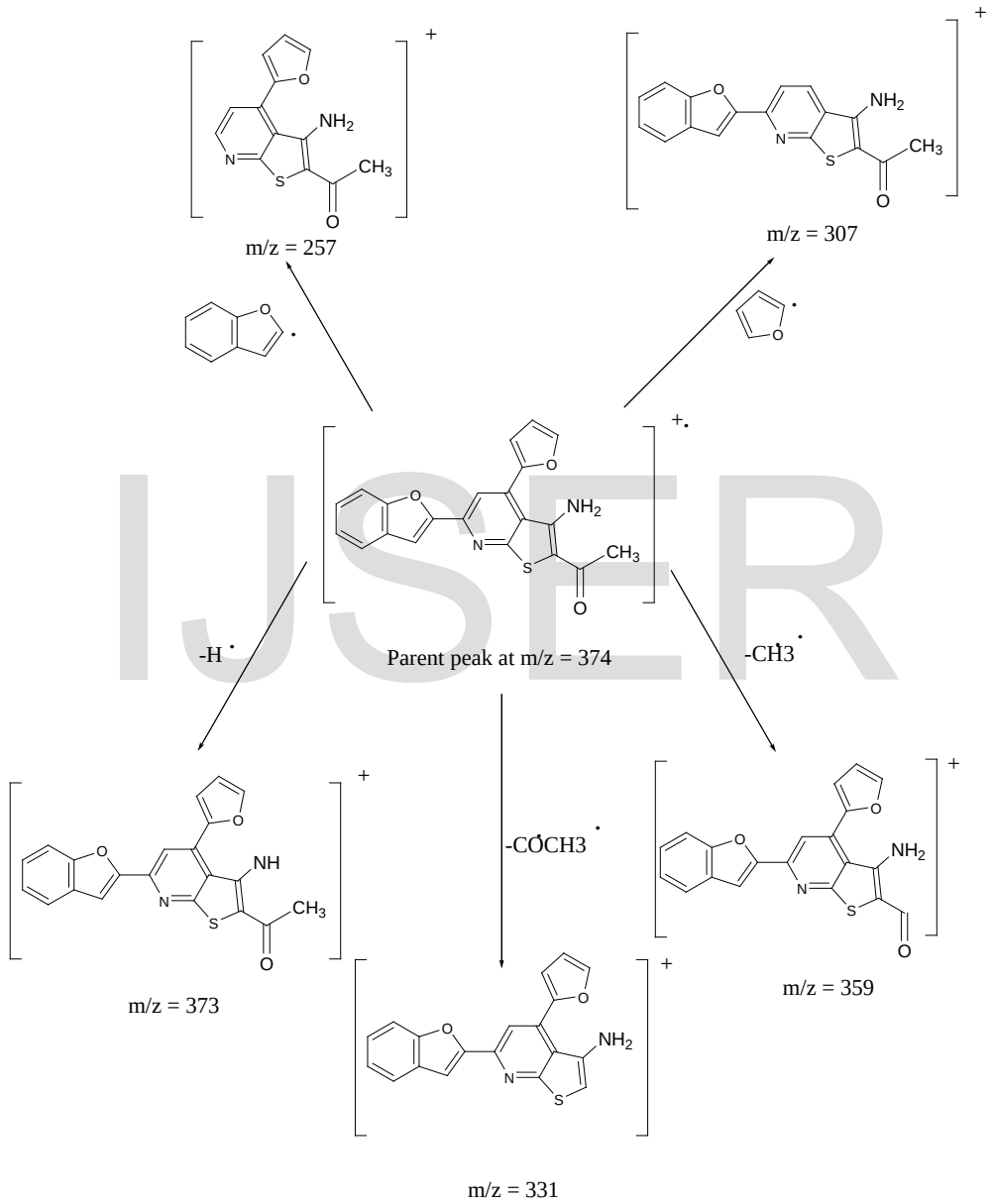
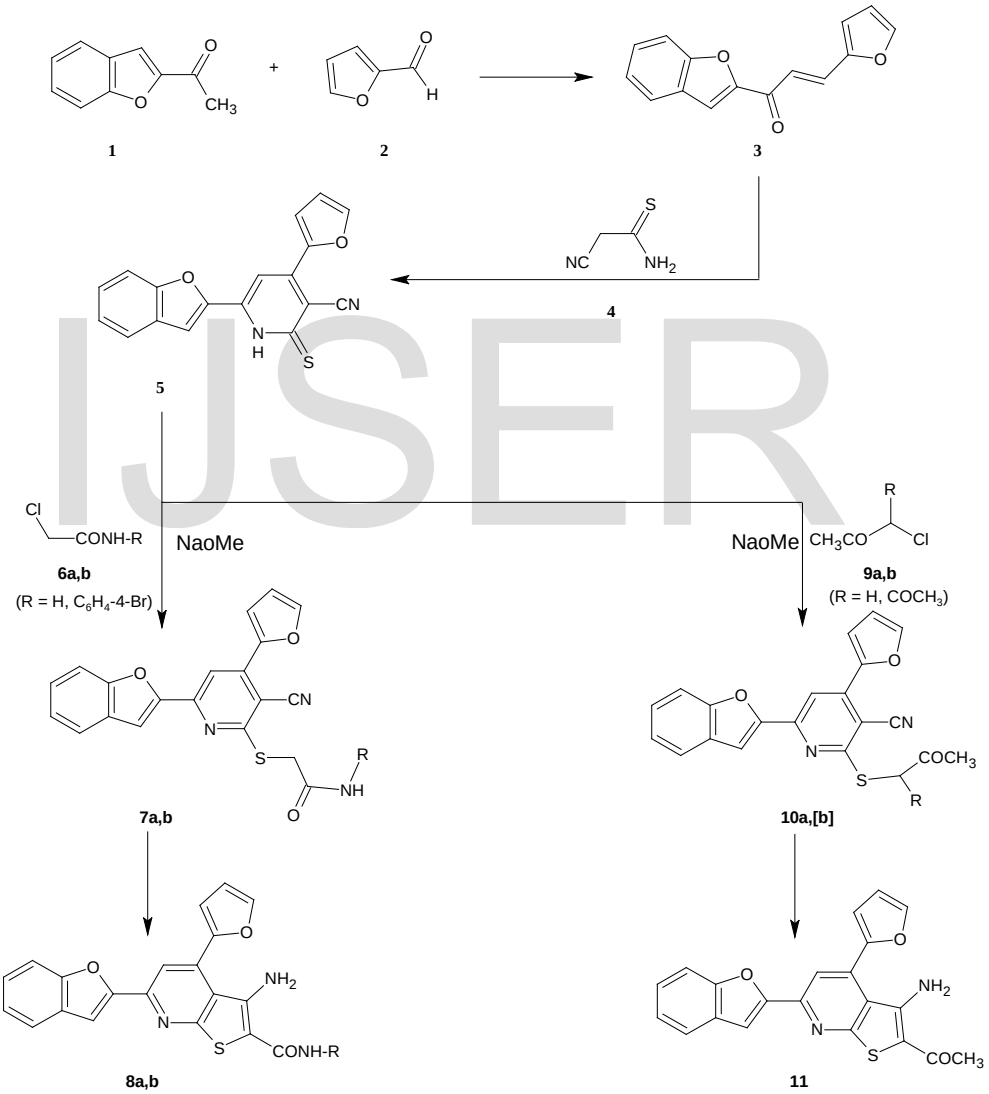
absorption bands corresponding CO and CN functions as well as its ^{1}H NMR revealed the signals of CO$\underline{CH_3}$, S$\underline{CH_2}$, furan, aromatic and pyridine protons (cf. Exp. Part and Scheme 1). Compound **10a** cyclized in ethanolic potassium hydroxide under reflux 5hr to afford the corresponding thieno[2,3-b]pyridine derivative**11** whose structure was established by considering the data of IR, ^{1}H NMR and elemental analyses,moreover, its mass spectrum showed the peaks according to the fragmentation pattern illustrated below.An authentic sample of compound **11** obtained through the reaction of compound **5** with 3-chloropentane-2,4-dione **(9b)** under the same experimental conditions. It is important to report here that all trials to isolate the intermediate **10b** were failed under a variety of experimental conditions (cf. Exp. Part and Scheme 1).

Fragmentation pattern of compound 10a:



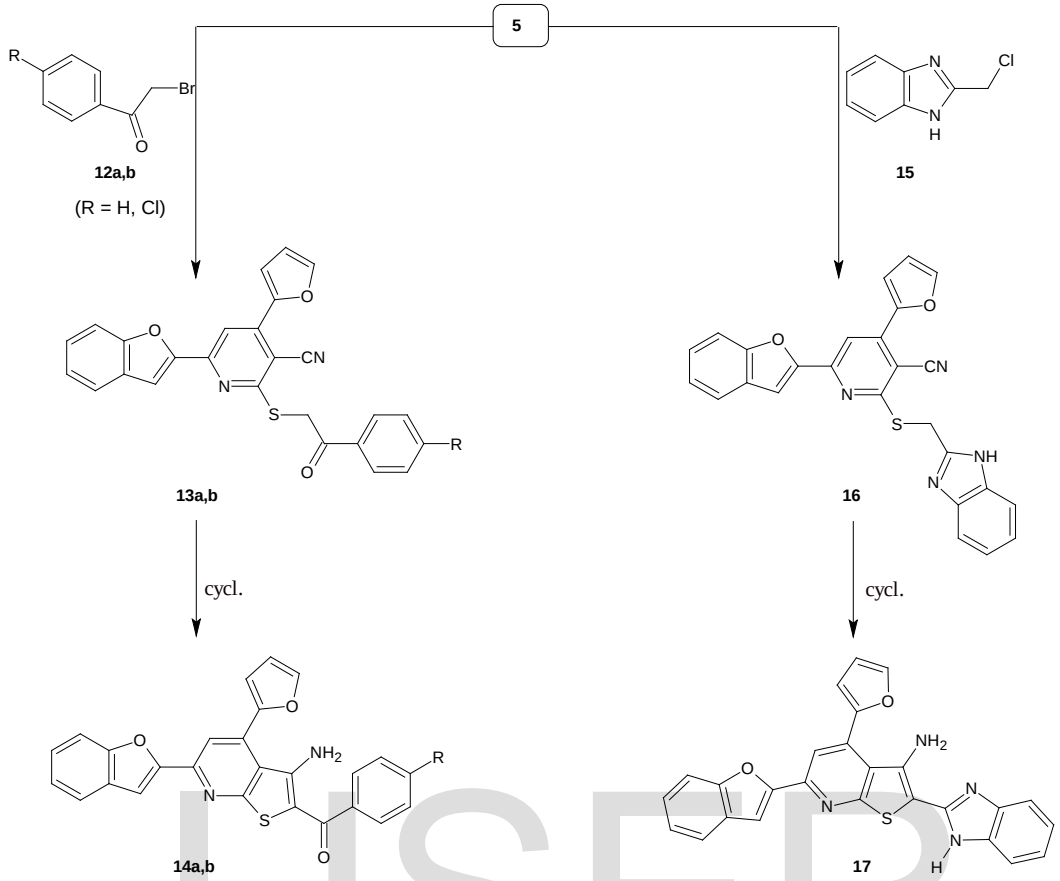
Similarly, Compound **5** was reacted with each of 2-bromo-1-(phenyl or 4-chlorophenyl)ethanone **(12a,b)** and chloromethylbenzimidazole **(15)** to afford 6-(1-benzofuran-2- yl)-2-{2-phenyl or 4-chlorophenyl-2-oxoethyl] or 2-[(1*H*-benzimidazol-2-ylmethyl)sulfanyl}-4-(furan-2-yl)-pyridine-3-carbonitriles **13a,b** and **16** respectively. Compounds **13a,b** and **16** were cyclized in respective manner to afford **14a,b** and **17** in ethanolic potassium hydroxide under reflux 5hr. The IR (cm^{-1}) of compounds **13a,b** and **16** showed the absorption bands of CN functions which disappeared from the IR (cm^{-1}) of compounds **14a,b** and **17** in addition to the absorption bands of NH_2 group for compounds **14a,b** and

17. Moreover, we elucidated the structures of each of compounds **13a,b**, **16**, **14a,b** and **17** by considering the data of ^{1}H NMR, mass spectra as well as that of elemental analyses(cf. Exp. Part and Scheme 2).The study was extended to explore the nucleophilic reactivity of SH group in compound **5** towards electrophilic C-containing reagents e.g. iodomethane and chloroacetonitrile **18a,b**. Thus, it has been found that compound **5** was reacted with iodomethane **(18a)** in methanolic sodium methoxide under stirring at room temperature for 30min. to give the corresponding 2-methylthio derivative **19a** whose structure was elucidated by considering the data of elemental analyses, IR and mass spectra (cf. Exp. Part). Also, compound **20** obtained without isolation of **19b** under a variety of reaction conditions through the reaction of compound **5** with chloroacetonitrile **(18b)** in methanolic sodium methoxide either at room temperature under stirring or under reflux for 3-5hr. The IR (cm^{-1}) of this reaction product showed the absorption bands of CN and NH_2functions andits mass spectrum gaveparent and base peak at m/z = 357 which corresponds to its molecular weight. Furthermore, peaks at m/z = 356, 355, 341 and 331 which corresponds to the fragments related to the removal of H, 2H, NH_2 and CN radicals from radical-cation ($M^{+\cdot}$) form of compound **20**. The ^{1}H NMR spectrum of this reaction product revealed the signals of NH_2, furan, pyridine and aromatic protons (cf. Scheme 3 and Exp. Part).



Scheme 1

Scheme 1: Synthesis of **7a,b**; **8a,b**; **10a** and **11** from pyridinethione derivative **5**



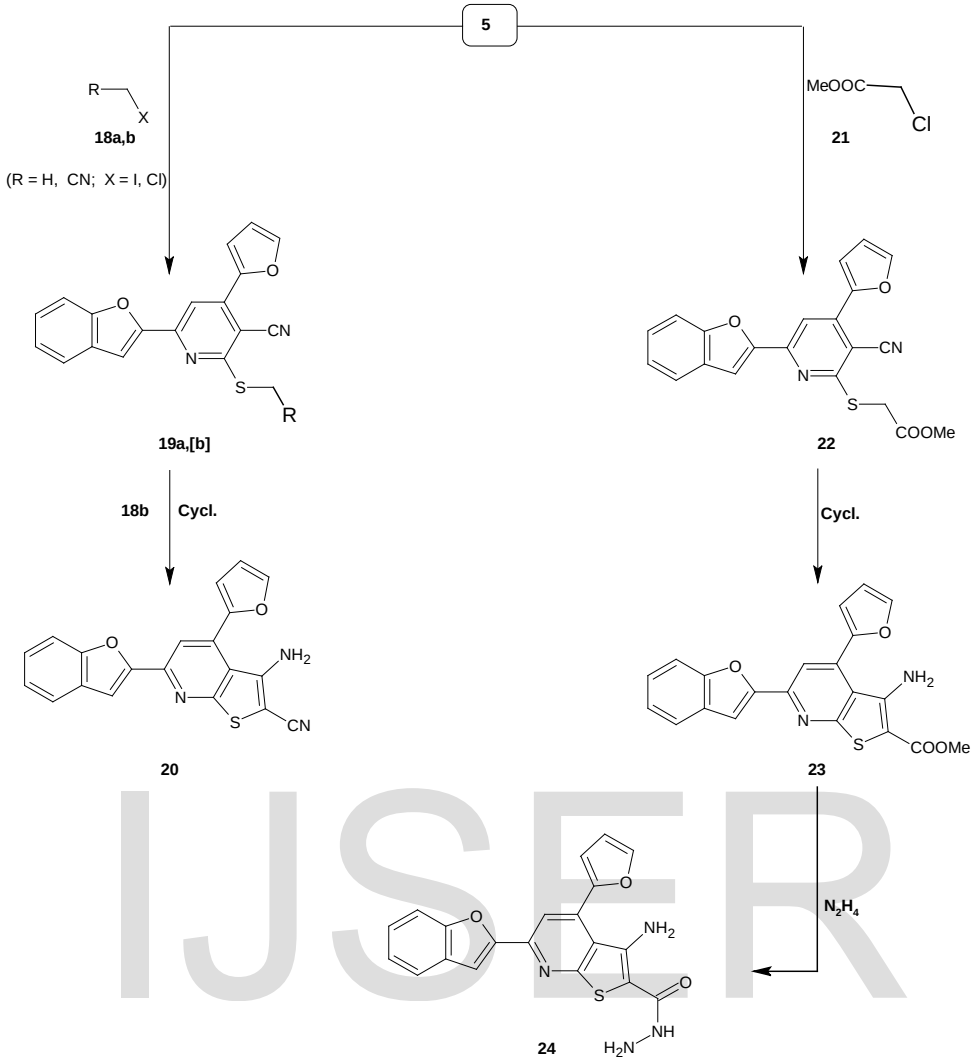
Scheme 2

Scheme 2: Synthesis of **13a,b**; **14a,b**; **16**; **17** from pyridinethione derivative **5**

Compound **5** was reacted with methyl chloroacetate **(21)** underthe same above-mentioned experimental conditions to afford the reaction product **22** which cyclized to the corresponding thieno[2,3-b]pyridine derivative **23**. The structure of both **22** and **23** was elucidated by considering the data of elemental analyses and spectral data studies (cf. Exp. Part and Scheme 3). Compound **23** was used as a good starting material to synthesize new synthon **24** through its reaction with hydrazine hydrate. The IR (cm^{-1}) of compound **24** showed the absorption bands of NH_2 and $NHNH_2$ as well as its ^1H NMR spectrum revealed the signals of NH_2, $NHNH_2$, furan, pyridine and aromatic protons. Moreover, its mass spectrum gave the parent peak (M^+) at m/z = 390 which corresponds to its molecular weight and peaks corresponds to the fragments at M^+-H, M^+-NH_2, M^+-$NHNH_2$, M^+-$CONHNH_2$ (cf. Exp. Part and Scheme 3).

The chemical reactivity and synthetic potentiality of **24** was investigated via its chemical reactions with several reagents. Thus, it has been found that **24** was reacted with each of pentan-2,4-dione **25**andethyl 3-oxobutanoate**27**in acetic acid under reflux for 3-5 hours to afford the reaction products**26 and 28.** ^{1}HNMR spectrum of **26** was found in good agreement with the assigned structure. Compound **24**was reacted with (benzylidene)malononitrile **(29)** or benzaldehyde **(30)** in pyridine-ethanol mixture under reflux to afford the reaction product formulated as **31** (cf. Scheme 4). The chemical structure of **31** was confirmed by considering the data of IR and elemental analyses. Moreover, its mass spectrum gave m/z = 478(38.2 %) which corresponding to its molecular weight, in addition to several peaks corresponding to fragments that confirm its structure. Also ^{1}HNMR spectrum of **31**was found in good agreement with the assigned structure (cf. Exp. Part and Scheme 4).

Compound **24** also, was reacted with each of formic acid, acetic anhydride, triethyl orthoformate, dimethylform-amide-dimethylacetal and glacial acetic acid in a respective manner to afford the corresponding pyridothieno-pyrimidines **33**, **35**, **38a, b** andpyrazolo[3',4':4,5]thieno[2,3-*b*]pyridin-3-one **40** respectively. The elemental analyses and IR spectral data considered to elucidate the structure of these products and their mass spectra confirm their structures further, it gave m/z = 400 (66.7 %) for **33**, 498(51.2%) for **35**, 456(16.5%) for **38a,** 455(14.6%) for **38b** and 415(36.8%) for **40** (cf. Scheme 4).



Scheme 3

Scheme 3: Synthesis of **19a; 20; 22; 23; 24** from pyridinethione derivative **5**

3 EXPERIMENTAL

All melting points were uncorrected. I.R. (KBr discs) spectra were recorded on a Shimadzu FTIR-8201PC Spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian Mercury 300 MHz., and a Varian Gemini 200 MHz. spectrometers using TMS as an internal standard and $CDCl_3$, DMSO-d_6, and $(CD_3)_2CO$ as solvents. Chemical shifts were expressed as δ (ppm) units. Mass spectra were recorded on Shimadzu GCMS-QP1000EX using an inlet type at 70 eV. The Micro analytical Center of Cairo University performed the microanalyses

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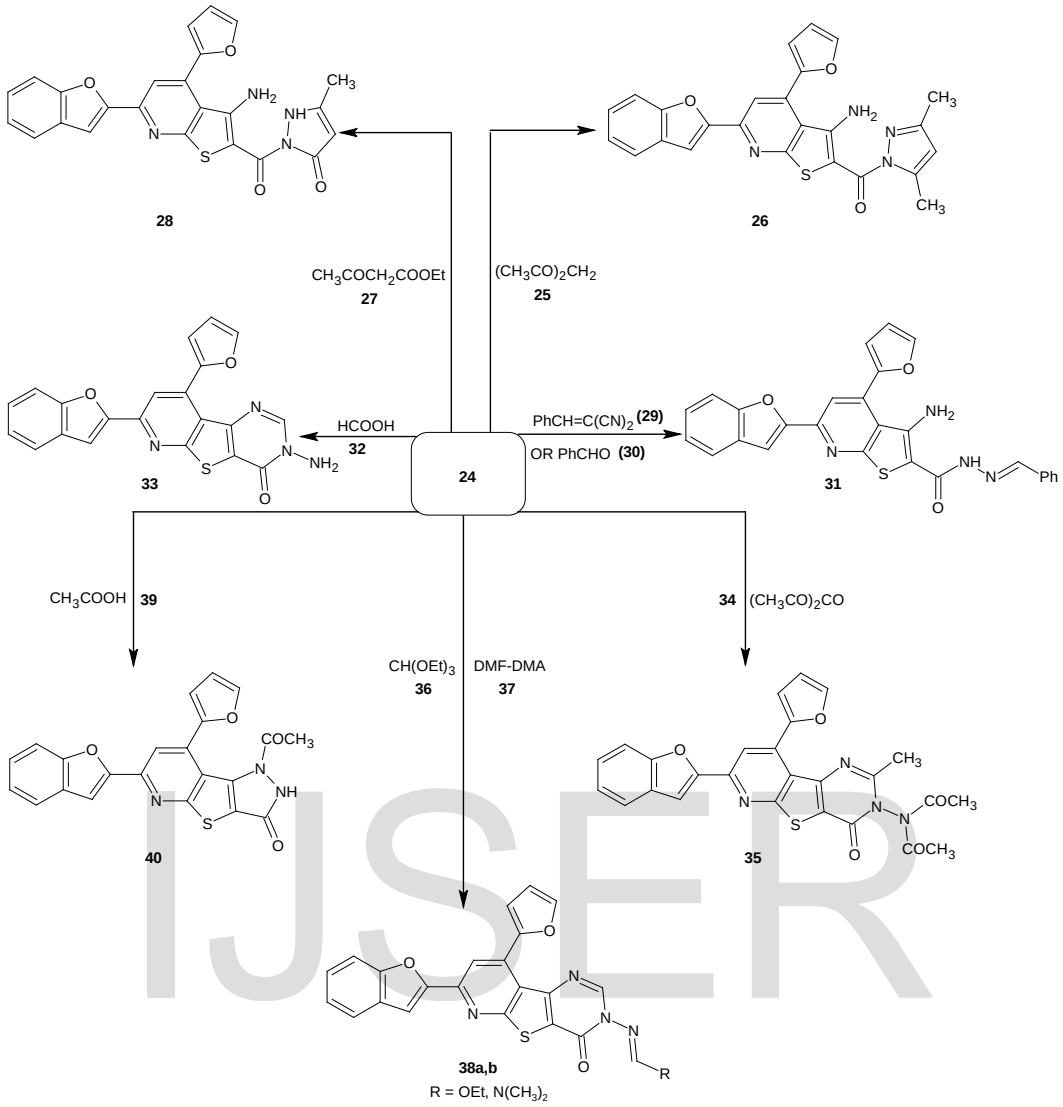

Scheme 4

Scheme 4: Synthesis of **26**; **28**; **31**; **33**; **35**; **38**; **40** from carbohydrazide derivative **24**

Synthesis of 5

A solution of each of **3** (2.38g, 10mmol) and **4** (1g, 10mmol) in absolute ethanol (30mL) and few drops of piperidine was added and heated under reflux for 5hrs. The reaction mixture was then evaporated till 1/3 volume then leave the solution about thirty minutes, the product so formed, was collected by filtration, washed with cold ethanol, and then crystallized from the dioxane to give the corresponding **5**.

6-(1-Benzofuran-2-yl)-4-(furan-2-yl)-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile5 : Orange crystals, m.p. 262°C; **IR** (***ν*cm⁻¹**): 3435(NH), 2219(CN) and 1557 (C= S); **MS** (m/z): 318 (M^+,98.5% corresponding to the molecular formula $C_{18}H_{10}N_2O_2S$ of the assigned structure), 319 (M^{+}+ 1, 19.1 %), 317 (M^{+}- H, 75.0 %), 293 (M^{+}+ 1 - CN, 100 %), 292 (M^+ -CN, 67.6%).**^{1}H NMR** (***δ*ppm**):6.74–8.245 (m, 10H, aromaticH's, C_5H and NH). Anal. for $C_{18}H_{10}N_2O_2S$ (318), Calcd./Found (%): C (67.91/67.82) H (3.17/3.00) N (8.80/8.52) S (10.07/9.80).

Synthesis of 7a,b, 10a, 13a,b, 16,19a, 20 and 22 : (General Procedure): A solution of each of **5** (0.318g, 1mmole) and2-Chloroacetamide**(6a)**, *N*-(4-bromophenyl)-2-chloro-acetamide**(6b),** chloroacetone **(9a),** 2-bromo-1-phenyl(4-chlorophenyl)ethanone **(12a,b),** chloromethylbenzimidazole **(15)**, methyl iodide(**18a**), chloroacetonitrile(**18b**) and methyl chloroacetate **(22)**, (0.093g, 0.248g, 0.092g, 0.166g, 0.284g,0.077g and 0.122g, 1 mmole) in sodium methoxide (prepared from 0.10 g of sodium and methanol 25 mL) was stirred at room temperature for 15 minutes. The formed precipitate was collected by filtration, washed with water crystallized from ethanol and dioxane to give **7a,b, 10a, 13a,b, 16,19a, 20** and **22** respectively.

2-{[6-(1-Benzofuran-2-yl)-3-cyano-4-(furan-2-yl)pyridin-2-yl]sulfanyl}-acetamide7a: Pale yellow crystals (75%), m.p = 264

°C; IR (cm^{-1}, KBr) υ: 3380, 3192(NH_2), 2214 (CN), 1649 (amidic CO); **MS**: 375 (M^+, 33.35% which corresponding to the molecular formula $C_{20}H_{13}N_3O_3S$ of the assigned structure), 359 (M^+ - NH_2, 1.87%) and 331 (M^+ -CO NH_2, 100%); Anal. Calcd. For $C_{20}H_{13}N_3O_3S$ (375): C 63.99 H 3.49 N 11.19 S 8.54. Found: C 63.83 H 3.31 N 11.10 S 8.42

2-{[6-(1-Benzofuran-2-yl)-3-cyano-4-(furan-2-yl)pyridin-2-yl]sulfanyl}-*N*-(4-bromophenyl)acetamide7b: Pale yellow crystals (75%), mp. = 250 °C; IR (cm^{-1}, KBr) υ: 3253(NH), 3034 (C-H aromatic), 2218 (CN), 1656 (amidic CO); ^{1}H NMR **(DMSO-d_6) δ (ppm):** 4.18 (s, 2H, -SCH_2-), 6.73- 7.95 (m, 13H, Ar, furyl and pyridinyl H's) and 10.61 (s, 1H, NH); Anal. Calcd. for $C_{26}H_{16}$ BrN_3O_3S (530): C 58.88 H 3.04 N 7.92 Br 15.07 S 6.05. Found: C 58.81 H 2.90 N 7.76 Br 14.80 S 6.00

6-(1-Benzofuran-2-yl)-4-(furan-2-yl)-2-[2-oxopropyl)sulfanyl]pyridine -3- carbonitrile 10a: Pale yellow crystals (68%), m.p = 184 °C; IR (cm^{-1}, KBr) υ: 3062 (C-H aromatic), 2214 (CN), 1720 (CO); ^{1}H NMR **(DMSO-d_6) δ (ppm):**2.37 (s, 3H, CH_3), 4.33 (s, 2H, -SCH_2-) and 6.71- 8.14 (m, 9H, Ar, furyl and pyridinyl H's); Anal. Calcd. For $C_{21}H_{14}N_2O_3S$ (374): C 67.37 H 3.77 N 7.48 S 8.56. Found: C 67.10 H 3.35 N 7.13 S 8.42

6-(1-Benzofuran-2-yl)-4-(furan-2-yl)-2-[2-oxo-2-phenylethyl)sulfanyl]pyridine-3- carbonitrile 13a: Orange crystals (55%), m.p = 120 °C; IR (cm^{-1}, KBr) υ: 2220 (CN), 1691 (CO);Anal. Calcd. For $C_{26}H_{16}N_2O_3S$ (436): C 71.54 H 3.69 N 6.42 S 7.35. Found: C 71.35 H 3.32 N 6.13 S 7.42

6-(1-Benzofuran-2-yl)-4-(furan-2-yl)-2-{[2-(4-chlorophenyl)-2-oxo-ethyl)]sulfanyl}pyridine-3-carbonitrile 13b: Pale yellow crystals (62/%), m.p = 150 °C; IR (cm^{-1}, KBr) υ: 2209 (CN), 1689(CO); ^{1}H NMR **(DMSO-d_6) δ (ppm):** 4.85 (s, 2H, -SCH_2-) and 6.68- 8.18 (m, 13H, Ar, furyl and pyridinyl H's); Anal. Calcd. For $C_{26}H_{15}ClN_2O_3S$ (471): C 66.31 H 3.21 N 5.95 S 6.81 Cl 7.53. Found: C 66.15 H 3.30 N 5.42 S 6.42 Cl 7.32

2-[(1*H*-Benzimidazol-2-ylmethyl)sulfanyl]-6-(1-benzofuran-2-yl)-4-(furan-2-yl)pyridine-3-carbonitrile 16: Pale yellow crystals (51/%), m.p = 254 °C; IR (cm^{-1}, KBr) υ: 3368(NH), 3049(Aromatics CH) and 2211 (CN);**MS**: 448(M^+, 80.8% which corresponding to the of the molecular formula $C_{26}H_{16}N_4O_2S$ of the assigned structure), 447 (M^+ -H, 54.9 %), 317 (M^+ - benzimidazolyl methyl, 8.3%), 163 (SCH_2benzimidazolyl, 100%) and 131(benzimidazolyl methyl, 77.7%); ^{1}H NMR **(DMSO-d_6) δ (ppm):** 4.90 (s, 2H, -SCH_2-) and 6.84- 8.11 (m, 14H, Ar, furyl, pyridinyl H's and NH); Anal. Calcd. For $C_{26}H_{16}N_4O_2S$ (448): C 69.63 H 3.60 N 12.49 S 7.15. Found: C 69.30 H 3.45 N 12.10 S 6.90

6-(1-Benzofuran-2-yl)-4-(furan-2-yl)-2-(methylsulfanyl)-pyridine-3- carbonitrile 19a: Pale yellow crystals (60%), m.p = 152 °C; IR (cm^{-1}, KBr) υ: 2210 (CN); Anal. Calcd. For $C_{19}H_{12}N_2O_2S$ (332): C 68.66 H 3.64 N 8.43 S 9.65. Found: C 66.35 H 3.42 N 8.30 S 9.42

3-Amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-b]-pyridine-2-carbonitrile20: Yellow crystals (65%), m.p = 228 °C; IR (cm^{-1}, KBr) υ: 3467, 3339(NH_2), 3027 (C-H, aromatic), 2195 (CN); **MS**: 357 (M^+, 100% which corresponding to the of the molecular formula $C_{20}H_{11}N_3O_2S$ of the assigned structure), 359 (M^+ - NH_2, 8.63%) and 331 (M^+ - CN, 45.12%)^{1}H NMR **(DMSO-d_6) δ (ppm):** 6.49 (s, 2H, NH_2) and 6.86- 8.14 (m, 9H, Ar, furyl, pyridinyl H's); Anal. Calcd. for $C_{20}H_{11}N_3O_2S$ (357): C 67.21 H 3.10 N 11.76 S 8.97. Found: C 67.10 H 2.90 N 11.60 S 8.63

Methyl {[6-(1-benzofuran-2-yl)-3-cyano-4-(furan-2-yl)-pyridin-2-yl]-sulfanyl}acetate 22: Pale yellow crystals (65 %), m.p = 172 °C; IR (cm^{-1}, KBr) υ: 3056(Aromatic CH), 2214 (CN) and 1742 (ester CO); ^{1}H NMR **(DMSO-d_6) δ (ppm):** 3.68 (s, 3H, $COOCH_3$),4.24 (s, 2H, -SCH_2-) and 6.73- 8.14 (m, 9H, Ar, furyl, pyridinyl H's); Anal. Calcd. For $C_{21}H_{14}N_2O_4S$ (390): C 64.60 H 3.61 N 7.18 S 8.21. Found: C 64.50 H 3.45N 6.80 S 8.00

Synthesis of8a,b, **11**, **14a,b**, **17** and **23**: A mixture of each of **7a,b, 10a, 13a,b, 16 and 22** (0.01 mole of each) and ethanolic sodium ethoxide (0.23g of sodium with about 50mL ethanol) was heated under reflux for 2h. The product so formed after cooling was filtered off, wash with water and crystallize from dioxane solvent to afford **8a,b**, **11**, **14a,b**, **17** and **23** respectively.

3-Amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-*b*]-pyridine-2-carboxamide 8a:Yellow crystals (75%), m.p=300 °C; IR (cm^{-1}, KBr) υ: 3469, 3318, 3261 3139(two NH_2), 1665 (amidic CO); H NMR **(DMSO-d_6) δ (ppm):** 6.81- 8.08 (m, 13H, Ar, furyl, pyridinyl H's and $2NH_2$);; Anal. Calcd. For $C_{20}H_{13}N_3O_3S$ (375): C 63.99 H 3.49 N 11.19 S 8.54. Found: C 63.72 H 3.30 N 11.00 S 8.34

3-Amino-6-(1-benzofuran-2-yl)-*N*-(4-bromophenyl)-4-(furan-2-yl)thieno[2,3-b]pyridine-2-carboxamide8b: White crystals (55%), m.p = 256 °C; IR (cm^{-1}, KBr) υ: 3251, 3120(NH_2), 3027 (C-H aromatic), 1656 (amidic CO); **MS**: 532(M^++2, 26.11%), 530 (M^+, 24.4% which corresponding to the of the molecular formula $C_{26}H_{16}$ BrN_3O_3S of the assigned structure), 359 (M^+ - NHPh-Br, 100%) and 331 (M^+ -CO NHPh-Br, 21.36%); Anal. Calcd. for $C_{26}H_{16}$ BrN_3O_3S (530): C 58.88 H 3.04 N 7.92 Br 15.07 S 6.05. Found: C 58.80 H 2.90 N 7.60 Br 14.75 S 5.90

1-[3-Amino-6-(1-benzofuran-2-yl) 4-(furan-2-yl)thieno[2,3-b]pyridine-2-yl]ethanone 11: Orange crystals (65%), m.p =>300 °C; IR (cm^{-1}, KBr) υ: 3476, 3300(NH_2), 1623 (CO with H-bonding);**MS**: 374(M^+, 100% which corresponding to the of the molecular formula $C_{21}H_{14}N_2O_3S$ of the assigned structure),373(M^+- H, 10 %), 359(M^+- CH_3, 70%), 331(M^+-$COCH_3$, 6%);^{1}H NMR **(DMSO-d_6) δ (ppm):** 2.42 (s, 3H, CH_3), 7.72 (br, 2H, NH_2)and 6.86- 8.10 (m, 9H, Ar, furyl and pyridinyl H's); Anal. Calcd. For $C_{21}H_{14}N_2O_3S$ (374): C 67.37 H 3.77 N 7.48 S 8.56. Found: C 67.10 H 3.50 N 7.23 S 8.30

[3-Amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-b]-pyridine-2-yl](phenyl)methanone14a: Orange crystals (50%), m.p = > 300 °C; IR (cm^{-1}, KBr) υ: 3466, 3400 (NH_2), 1637 (CO with H-bonding);Anal. Calcd. For $C_{26}H_{16}N_2O_3S$ (436): C 71.54 H 3.69 N 6.42 S 7.35. Found: C 71.20 H 3.50 N 6.23 S 7.20

[3-Amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-b]-pyridine-2-yl](4-chlorophenyl)methanone14b: Orange crystals (58%), m.p = > 300°C; IR (cm^{-1}, KBr) υ: 3475, 3277(NH_2);**MS**: 471(M^+,62.76 % which corresponding to the of the molecular formula $C_{26}H_{15}ClN_2O_3S$ of the assigned structure),470(M^+-H, 100 %),469(M^+- 2H, 95.82%), 359(M^+- Ph-Cl, 3.34%), 331(M^+- COPh-Cl, 4.42%, 139(COPh-Cl, 45.13%) and

111(Ph-Cl, 60.86%)Anal. Calcd. For $C_{26}H_{15}ClN_2O_3S$ (471): C 66.31 H 3.21 N 5.95 S 6.81 Cl 7.53. Found: C 66.20 H 3.15 N 5.32 S 6.70 Cl 7.22

2-(1*H*-Benzimidazol-2-yl)-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno-[2,3-b]pyridin-3-amine 17:Orange crystals (60/%), m.p = >300 ˚C; IR (cm^{-1}, KBr) υ: 3433, 3339, 3242(NH), ^{1}H NMR **(DMSO-d_6) δ (ppm):** 3.48 (br, 3H, NH_2 and NH) and 6.85- 8.09 (m, 13H, Ar, furyl, pyridinyl H's); Anal. Calcd. For $C_{26}H_{16}N_4O_2S$ (448): C 69.63 H 3.60 N 12.49 S 7.15. Found: C 69.45 H 3.50 N 12.25 S 7.10

Ethyl 3-amino-(6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno-[2,3-b]-pyridine-2- carboxylate 23: Yellow crystals (55 %), m.p = >300˚C; IR (cm^{-1}, KBr) υ:3433, 3300 (NH_2) and 1665 (ester CO with H-bonding); ^{1}H NMR **(DMSO-d_6) δ (ppm):** 3.30 (s, 3H, $COOCH_3$), 6.30(s, 2H, NH_2) and 6.78- 8.03 (m, 9H, Ar, furyl, pyridinyl H's); Anal. Calcd. For $C_{21}H_{14}N_2O_4S$ (390): C 64.60 H 3.61 N 7.18 S 8.21. Found: C 64.35 H 3.60 N 7.10 S 7.90

Synthesis of hydrazide 24:Method A: A solution of **22** (0.0025 mol) in hydrazine hydrate (15mL) and ethanol (20 mL) was heated under reflux for 5 h; the excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **24**.

Method B: A solution of **23** (0.0025 mol) in hydrazine hydrate (15mL) and ethanol (20 mL) was heated under reflux for 4 h; the excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **24**.

3-Amino-6--(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-*b*]pyridine-2-carbohydrazide(24): Yellow crystals (76%), m.p= 265◦C; **IR** (νcm^{-1}): 3450, 3301, 3124 (NH & NH_2), **MS**: 390 (M^+, 27.1% which corresponding to the of the molecular formula $C_{20}H_{14}N_4O_3S$ of the assigned structure), 359 (M^+-$NHNH_2$, 100%), 331 (M^+-$CONHNH_2$, 13.7%); **^{1}H NMR** (DMSO-D_6) (δppm): 4.31 (br, 2H, NH_2); 4.48 (br, 2H, NH_2); 6.73-8.07 (m, 9H, Aromatic HS) and 9,40 (br, 1H, NH);Anal. Calcd. For$C_{20}H_{14}N_4O_3S$ (390): C 61.53 H 3.61 N 14.35 S 8.21. Found: C 61.40 H 3.50 N 14.23 S 8.10

Synthesis of 26: A solution of **24** (0.2g, 0.00055 mol) in acetylacetone **25** (10 mL) was heated under reflux for 6 h. The reaction mixture was triturated with ethanol (5mL) and then left to cool. The solid was collected by filtration, dried and crystallized from the dioxane to give **26.**

2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-(furan-2-yl)-6-(1-benzo-furan-2-yl)thieno[2,3-*b*]pyridin-3-amine (26): Red crystals (87%), m.p= >300◦C; **IR** (νcm^{-1}): 3436, 3337 (NH_2), 3031 (aromatic-CH), 1640 (CO);**^{1}H NMR** (DMSO-D_6) (δppm): 2.29(s, 3H,CH_3); 2.49(s, 3H,CH_3);6.23(s, 2H, NH_2) and 6.86- 8.09(m, 10H, ArHs, and hetero-ArHs);Anal. Calcd. For $C_{25}H_{18}N_4O_3S$ (454): C 66.07 H 3.99 N 12.33 S 7.05. Found: C 65.80 H 3.84 N 12.10 S 7.10

Synthesis of 27: A solution of **24** (0.2g, 1mmol) with ethyl acetoacetate (0.12g, 1mmol) in acetic acid (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and the solid so formed after cooling was collected by filtration, dried and crystallized from the acetic acid to give **27**.

2-{[3-amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)thieno[2,3-*b*]pyridin-2-yl]carbonyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one: Orange crystals (67%), m.p= >300◦C; **IR** (νcm^{-1}): 3435, 3338 (NH_2), 3104(NH), 1673, 1615 (two CO); Anal. Calcd. For $C_{24}H_{16}N_4O_4S$ (456): C 63.15 H 3.53 N 12.27 S 7.02. Found: C 62.90 H 3.20 N 12.10 S 6.90

Synthesis of 31: Method A: A solution of **24** (0.2 g, 0.00055 mol) and benzylidenemalononitrile **29**(0.1g, 0.00055 mol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 2 h, the excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the dioxane to give **31**.

Method B: A solution of **24**(0.20g, 0.00055 mol) and benzaldehyde **30** (0.058g, 0.00055 mol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 2 h. Excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from dioxane to give **31**.

3-Amino-6-(1-benzofuran-2-yl)-4-(furan-2-yl)-*N*'-[(phenyl)-methyl-idene]thieno[2,3-*b*]pyridine-2-carbohydrazide (31): Red crystals (86%), m.p= 285◦C; **IR** (νcm^{-1}): 3481, 3305 (NH_2), 3125 (NH), 3034 (aromatic-CH) and 1631 (amidic CO); **MS**: 478 (M^+, 38.2% which corresponding to the molecular formula $C_{27}H_{18}N_4O_3S$ of the assigned structure), 359 (M^+ -NHN=CH-C_6H_5, 100%), 331 (M^+ -CONHN=CH-C_6H_5, 8.4%) ; **^{1}H NMR** (DMSO-D_6) (δppm): 6.83 (s, 2H, NH_2); 7.27- 8.05 (m, 13H, Aromatic Hs); 8.16 (s, 1H, -N=CH) and 11.39 (br, 1H, NH); Anal. Calcd. For $C_{27}H_{18}N_4O_3S$ (478): C 67.77 H 3.79 N 11.71 S 6.70. Found: C 67.65 H 3.54 N 11.53 S 6.61

Synthesis of 33: A solution of **24** (0.2g, 0.00055 mol) and formic acid **32** (15 ml) was heated under reflux for 6 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **33**.

3-Amino-7-(1-benzofuran-2-yl)-9-(furan-2-yl)pyrido[3',2'-:4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-one 33:Yellow crystals (87%), m.p= 308◦C;**IR** (νcm^{-1}): 3435, 3245 (NH_2) and 1666 (amidic CO); **MS**: 400 (M^+, 66.7% which corresponding to the molecular formula $C_{21}H_{12}N_4O_3S$ of the assigned structure) and 384 (M^+ -NH_2, 55.6%), **^{1}H NMR** (DMSO-D_6) (δppm): 6.16- 8.67 (m, 12H, NH_2, Aromatic, furyl Hs and C_2H); Anal. Calcd. For $C_{21}H_{12}N_4O_3S$ (400): C 62.99 H 3.02 N 13.99 S 8.01 Found: C 62.65 H 3.00 N 13.63 S 7.80

Synthesis of 35: A solution of **24** (0.2g, 0.00055 mol) and acetic anhydride **34** (15 ml) was heated under reflux for 6 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from dioxane to give **35**.

***N*-Acetyl-*N*-(7-(1-Benzofuran-2-yl)-9-(furan-2-yl)-2-methyl-4-oxopyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidin-3(*4H*)-yl)aceta-mide35:** Yellow crystals (78%), m.p= 275◦C; **IR** (νcm^{-1}): 1743, 1687 (CO); **MS**: 498 (M^+, 51.2% which corresponding to the molecular formula $C_{26}H_{18}N_4O_5S$ of the assigned

structure), 497 (M^+ -H, 42.2%), 455 (M^+ -$COCH_3$, 59.5%), 412 (M^+ -2$COCH_3$, 6.4%), 398 (M^+ -N $(COCH_3)_2$, 19.7%); **^{1}H NMR** (DMSO-D_6) (δppm): 2.16(s,3H, CH_3); 2.45(s,3H, $COCH_3$); 2.50 (s,3H,$COCH_3$) and 6.84- 8.44 (m, 9H, Aromatic, furyl Hs); Anal. Calcd. For $C_{26}H_{18}N_4O_5S$ (498): C 62.64 H 3.64 N 11.24 S 6.43 Found: C 62.70 H 3.50 N 11.10 S 6.20

Synthesis of 36a

A solution of **24** (0.2g, 0.00055 mol) and triethyl-orthoforrmate **36** (10mL) was heated under reflux for 4 h. The excess triethylorthoforrmate was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from dioxane to give **38a**.

Ethyl [7-(1-Benzofuran-2-yl)-9-(furan-2-yl)-4-oxopyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidin-3(4*H*)-yl] imidoformamide 38a: Yellow crystals (58%), m.p= >300◦C; **IR** (νcm^{-1}): 3048 (Aromatic CH), 1678 (CO); **MS**: 456 (M^+, 16.5% which corresponding to the molecular formula $C_{24}H_{16}N_4O_4S$ of the assigned structure), 455 (M^+ -H, 5.2%), 441 (M^+ -CH_3, 56.5%), 385(M^+ - N=C-OCH_2CH_3,100 %) and 384 (M^+ -N=CH-OCH_2CH_3,53.9%); **^{1}H NMR** (DMSO-D_6) (δppm): 1.40(t, 3H,$OCH_2\underline{CH_3}$); 4.40 (q, 2H, $O\underline{CH_2}$ CH_3)and 6.85-8.79 (m, 11H, Aromatic Hs, C_2H and N=<u>CH</u>); Anal. Calcd. For $C_{24}H_{16}N_4O_4S$ (456): C 63.15 H 3.53 N 12.27 S 7.02 Found: C 63.00 H 3.40 N 11.90 S 6.82

Synthesis of 38b: A solution of **24** (0.2g, 0.00055 mol) and dimethylformamide-dimethylacetal **37**(0.07g, 0.00055 mol) in dry xylene (15 ml) was heated under reflux for 5 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from dioxane to give **38b**.

***N*-[7-(1-Benzofuran-2-yl)-9-(furan-2-yl)-4-oxopyrido[3',2'-:4,5]thieno-[3,2-*d*]-pyrimidin-3(4*H*)-yl]N, N-dimethyl-imidoformamide 38b:** Pale yellow crystals (68%), m.p= 294◦C; **IR** (νcm^{-1}): 3059 (Aromatic CH), 1667 (CO); **MS**: 455 (M^+, 14.6% which corresponding to the molecular formula $C_{24}H_{17}N_5O_3S$ of the assigned structure), 454 (M^+ -H, 11%), 411 (M^+ -N$(CH_3)_2$, 1.4%), 384 (M^+ - N=CH-N$(CH_3)_2$,46.8%); **^{1}H NMR** (DMSO-D_6) (δppm): 3.03(s,6H,N$(CH_3)_2$); and 6.81-8.52 (m, 11H, Aromatic Hs, C_2H and N=<u>CH</u>); Anal. Calcd. For $C_{24}H_{17}N_5O_3S$ (455): C 63.29 H 3.76 N 15.38 S 7.04 Found: C 62.90 H 3.50 N 15.10 S 6.80

1-Acetyl-6-(1-benzofuran-2-yl)-8-(furan-2-yl)-1,2-dihydro-3*H*-pyraz-olo[3',4':4,5]thieno[2,3-*b*]pyridin-3-one40: Orange crystals (58%), m.p= 320◦C; **IR** (νcm^{-1}): 3482, 3140(two NH), 1669 (CO); **MS**: 415 (M^+, 36.8% which corresponding to the molecular formula $C_{22}H_{13}N_3O_4S$ of the assigned structure), 414 (M^+ -H, 36.8 %); **^{1}H NMR** (DMSO-D_6) (δppm): 2.73(s, 3H,$COCH_3$), 6.05- 8.60 (m, 9H, Aromatic, furyl Hs) and 10.59 (s, 1H, NH); Anal. Calcd. For$C_{22}H_{13}N_3O_4S$ (415): C 63.61 H 3.15 N 10.12 S 7.72 Found: C 63.30 H 2.91 N 10.10 S 7.80

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