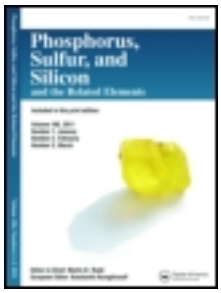

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Some Reactions of 2-Functionalized 3-Amino-4-aryl-6-(2′-thienyl)-thieno[2,3-b]pyridines: Synthesis of New Pyridothienopyrimidines, Pyridothienotriazines and Related Fused Tetracyclic Systems

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Version of record first published: 27 Oct 2010

To cite this article: A. E. Abdel-Rahman, E. A. Bakhite, O. S. Mohamed & E. A. Thabet (2003): Some Reactions of 2-Functionalized 3-Amino-4-aryl-6-(2′-thienyl)-thieno[2,3-b]pyridines: Synthesis of New Pyridothienopyrimidines, Pyridothienotriazines and Related Fused Tetracyclic Systems, Phosphorus, Sulfur, and Silicon and the Related Elements, 178:1, 89-106

To link to this article: http://dx.doi.org/10.1080/10426500307820

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:89–106

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390170228

SOME REACTIONS OF 2-FUNCTIONALIZED 3-AMINO-4-ARYL-6-(2′-THIENYL)-THIENO[2,3-B]-PYRIDINES: SYNTHESIS OF NEW PYRIDOTHIENOPYRIMIDINES, PYRIDOTHIENOTRIAZINES AND RELATED FUSED TETRACYCLIC SYSTEMS

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(Received June 4, 2002; accepted July 4, 2002)

*4-Aryl-3-cyano-6-(2′-thienyl)-pyridine-2(1*H*)-thiones (**2a–c**) were prepared and reacted with chloroacetonitrile or chloroacetamide to furnish 3-amino-4-aryl-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carbonitriles (**4a–c**) and 2-carboxamide analogs **6a–c** respectively. The reaction of **4a** and **6a–c** with a variety of reagents namely, formamide, carbon disulfide, phenyl isothiocyanate, ethylene diamine, sodium azide, triethyl orthoformate, and nitrous acid have been carried out and their products were identified. Most of these products were subjected to further reactions to obtain the rest of the title compounds.*

Keywords: Fused heterocyclic systems; pyridothienopyrimidines; pyridothienotriazines

INTRODUCTION

Thieno[2,3-b]pyridine ring system has proved to be an interesting class of heterocycles. It has been reported that many of its derivatives posses considerable antibaterial,[1,2] antiviral,[3] antihypertensive,[4] and gonadotropin-releasing hormone antagonizing[5,6] activity. Pyridothienopyrimidine derivatives have found applications as analgesics,[7] antipyretics,[8] and antiinflammatories.[9] Also, some pyridothienotriazines are reported to exhibit antianaphylactic[10] and antiallergic[11] activity. In view of these benefits and as a continuation of our previous work on condensed thienopyridines,[12–14] we undertook the synthesis of the title compounds.

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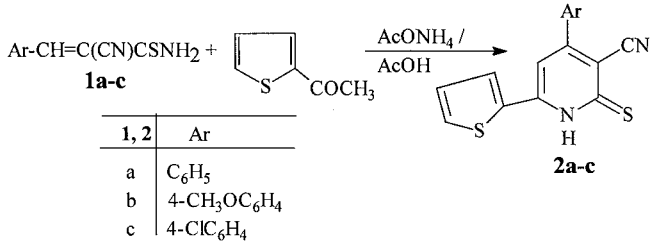
RESULTS AND DISCUSSION

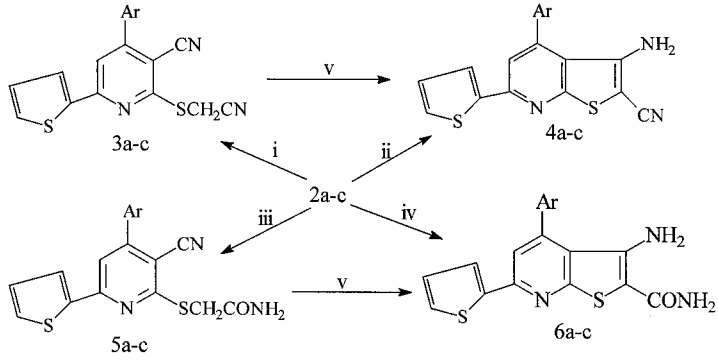
The starting compounds,4-aryl-3-cyano-6-(2′-thienyl)-pyridine-2(1*H*)-thiones (**2a–c**) were synthesized from the reaction of β-aryl-α-thiocarbamoylacrylonitriles (**1a–c**) with 2-acetylthiophene in the presence of ammonium acetate.



1, 2	Ar
a	C_6H_5
b	4-$CH_3OC_6H_4$
c	4-ClC_6H_4

SCHEME 1

The reaction of **2a–c** with chloroacetonitrile or chloroacetamide in the presence of sodium acetate gave 2-substituted methylthio-4-aryl-3-cyano-6-(2′-thienyl)-pyridines (**3a–c** and **5a–c**). Upon treatment of these compounds with sodium ethoxide in ethanol, they underwent intramolecular Thorpe-Ziegler cyclization to furnish 2-functionalized 3-amino-4-aryl-6-(2′-thienyl)-thieno[2,3-b]pyridines (**4a–c** and **6a–c** respectively). The latter thienopyridines were also prepared via direct reaction of **2a–c** with the appropriate halo compounds in the presence of sodium ethoxide as a basic catalyst (Scheme 2).

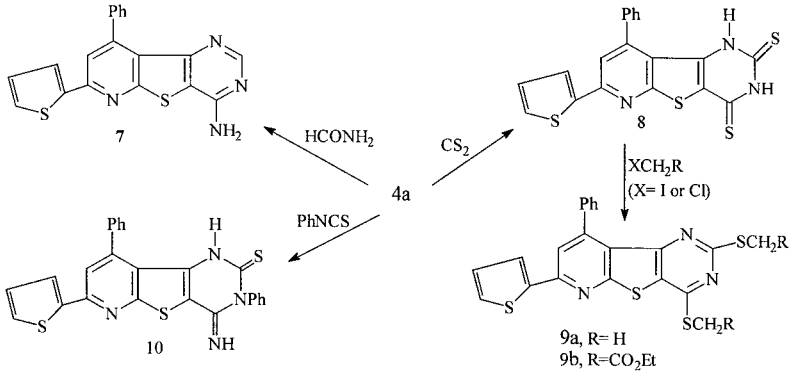


i: $ClCH_2CN$ /AcONa; ii: $ClCH_2CN$ / EtONa;
iii:$ClCH_2CONH_2$ / AcONa;
iv: $ClCH_2CONH_2$ / EtONa:;
v: EtONa / EtOH

3-6	Ar
a	Ph
b	4-$MeOC_6H_4$
c	4-ClC_6H_4

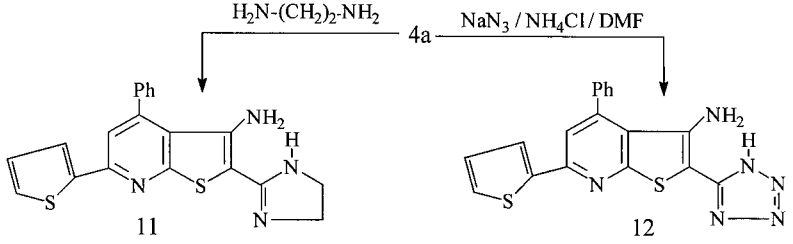
SCHEME 2

Heating **4a** with formamide at reflux temperature gave 4-amino-9-phenyl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (**7**). The interaction of **4a** with carbon disulfide in hot pyridine produced the pyrimidinedithione derivative **8** which in turn was reacted with methyl iodide or ethyl chloroacetate to furnish 2,4-disubstituted thiopyrimidines **9a** and **9b** respectively. When **4a** was allowed to react with phenyl isothiocyanate in hot pyridine, the 4-imino-3,9-diphenyl-1,2,3,4-tetrahydro-7-(2′-thienyl)-2-thioxopyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine (**10**) was obtained in high yield (Scheme 3).



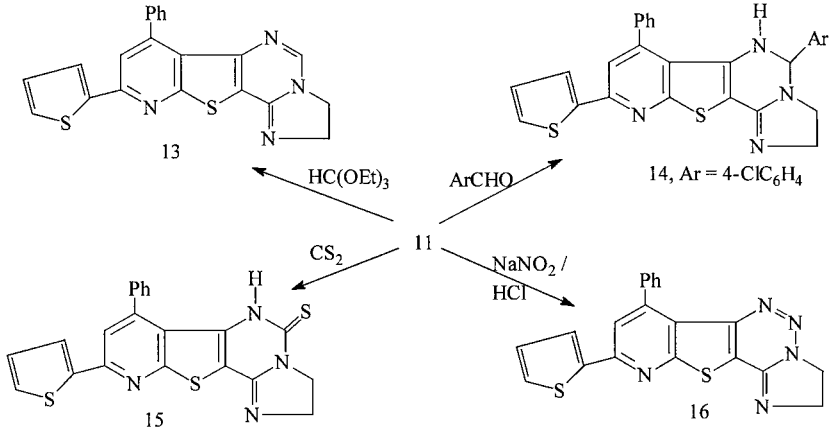
SCHEME 3

Incorporating the imidazolyl or tetrazolyl moiety into thienopyridine structure was successfully attempted by converting the nitrile group of **4a** into dihydroimidazolyl or tetrazolyl residue followed by subsequent reactions. Thus, the reaction of **4a** with ethylene diamine in the presence of a catalytic amount of carbon disulfide gave a good yield of 3-amino-2-(4,5-dihydroimidazol-2-yl)-4-phenyl-6-(2′-thienyl)-thieno[2,3-b]pyridine (**11**). On treatment of **4a** with sodium azide and ammonium chloride in hot DMF followed by acidification resulted in the formation of the tetrazolyl compound **12** (Scheme 4).



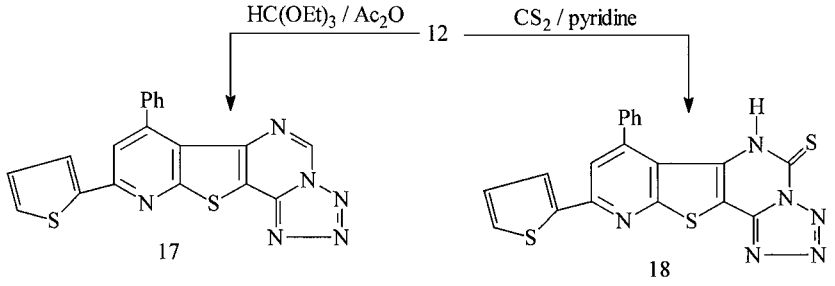
SCHEME 4

The reaction of **11** with triethyl orthoformate, *p*-chlorobenzaldehyde, and/or carbon disulfide gave imidazolo[1″,2″-c]pyrido[3′,2′:4,5]-thieno[2,3-e]pyrimidine derivatives **13**, **14** and **15** respectively. On treatment of **11** with nitrous acid, it underwent diazotization followed by self coupling to furnish **7**-phenyl-9-(2′-thienyl)-2,3-dihydroimidazolo[1″,2″-c]pyrido[3′,2′:4,5]thieno[3,2-e][1,2,3]triazine (**16**) in excellent yield (Scheme 5).



SCHEME 5

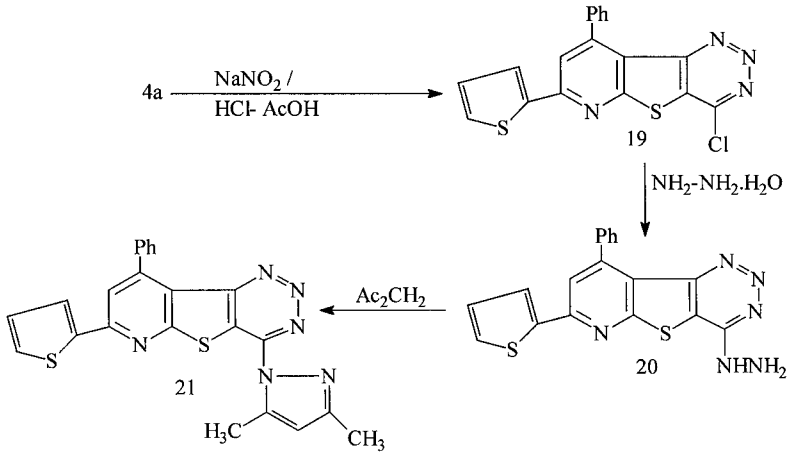
In the same manner, the compound **12** was reacted with triethyl orthoformate in the presence of acetic anhydride or with carbon disulfide in hot pyridine to afford the fused tetracyclic compounds **17** and **18** respectively (Scheme 6).



SCHEME 6

Diazotization of **4a** using sodium nitrite and HCl-AcOH mixture gave 4-chloro-9-phenyl-7-(2′-thienyl)-pyrido[3′,2,:4,5]thieno[3,2-d][1,2,3]triazine (**19**). The reaction of **19** with hydrazine hydrate

produced the hydrazino compound **20** which was cyclocondensed with acetylacetone to furnish the dimethylpyrazolyl derivative **21** (Scheme 7).



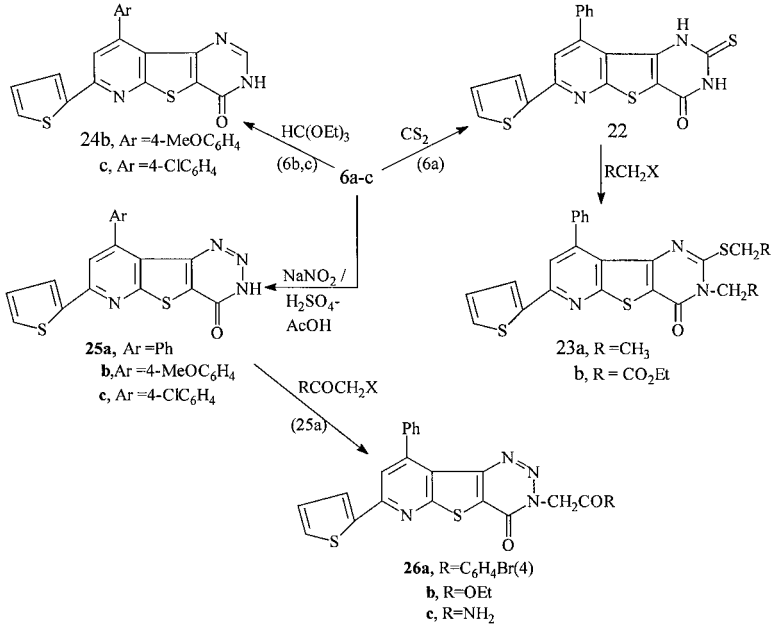
SCHEME 7

On the other hand, the interaction of **6a** with carbon disulfide in hot pyridine led to the formation of thioxopyrimidinone derivative **22**. When the latter compound was allowed to react with ethyl iodide or ethyl chloroacetate in DMF containing anhydrous K_2CO_3, the dialkylated products **23a**,**b** were obtained. The compounds **6b**,**c** were reacted with triethyl orthoformate in the presence of acetic anhydride to furnish 9-aryl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (**24b**,**c**). Treatment of compounds **6a–c** in AcOH—H_2SO_4 mixture with sodium nitrite solution at low temperature resulted in the formation of 1,2,3-triazinone derivatives **25a–c**. The N-alkylation of **25a** was achieved upon reaction with some halo compounds viz *p*-bromophenacy bromide, ethyl chloroacetate and chloroacetamide where the N-alkylated triazinone derivatives **26a–c** were obtained (Scheme 8).

The structures of all newly synthesized compounds were confirmed by elemental analyses, IR, ^{1}H NMR, and mass spectral data (cf. Experimental).

EXPERIMENTAL

All m.p.s are uncorrected and measured on a Gallenkamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr;



SCHEME 8

V_{max} in cm^{-1}); ^{1}H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard (δ in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on a Perkin-Elemer 240C elemental analyser or on an Elementar Analysensystem GmbH VARIOEL V2.3 July 1998 CHNS Mode.

4-Aryl-3-cyano-6-(2′-thienyl)pyridine-2(1*H*)-thiones (2a–c)

A mixture of β-aryl-α-thiocarbamoylacrylonitrile (**1a–c**) (20 mmol), ammonium acetate (4.0 g) and 2-acetylthiophene (2.18 ml, 20 mmol) in glacial acetic acid (25 ml) was heated under reflux for 48 h. The reaction mixture was evaporated under reduced pressure until dried, washed thorughly with water, and then treated with methanol. The separated solid was filtered off and crystallized from acetic acid as orange crystals of **2a–c**.

3-Cyano-4-phenyl-6-(2′-thienyl)-pyridine-2(1*H*)-thione (2a)

Prepared from **1a**. Yield: 43%; m.p.: 245°C. Anal. Calcd. for $C_{16}H_{10}N_2S_2$ (294.40): C, 65.28; H, 3.42; N, 9.52; S, 21.78%. Found: C, 65.00; H, 3.11;

N, 9.76; S, 21.39%. IR: $\nu = 3190–3180$ (NH), 2210 (CN) cm^{-1}. ^1H NMR (DMSO): $\delta = 8.3$ (m, 1H, CH thienyl), 7.6–8.2 (m, 6H: 5 ArH's and CH pyridine), 7.3 (m, 1H, CH thienyl), 7.1 (m, 1H, CH thienyl) ppm. MS: m/z = 294 (M^+, 100%), 250 (M^+-CS, 37%), 261 (M^+-SH, 30%), 77 ($C_6H_5^+$, 7%), 44 (CS^+, 3%).

3-Cyano-4-(*p*-methoxyphenyl)-6-(2′-thienyl)-pyridine-2(1*H*)-thione (2b)

Prepared from **1b**. Yield: 62%; m.p.: 250°C. Anal. Calcd. for $C_{17}H_{12}N_2OS_2$ (324.42): C, 62.94; H, 3.73; N, 8.63; S, 19.77%. Found: C, 62.53; H, 3.43; N, 8.90; S, 19.65%. IR: $\nu = 3190–3180$ (NH), 2210 (CN) cm^{-1}. ^1H NMR (TFA): $\delta = 7.8–8.2$ (m, 5H: 2 ArH's, 2CH thienyl and CH pyridine), 7.2–7.5 (m, 3H: 2 ArH's and CH thienyl), 4.0 (s, 3H, OCH_3) ppm.

4-(*p*-Chlorophenyl)-3-cyano-6-(2′-thienyl)-pyridine-2(1*H*)-thione (2c)

Prepared from **1c**. Yield: 47%; m.p.: 242°C. Anal. Calcd. for $C_{16}H_9ClN_2S_2$(329.86): C, 58.44; H, 2.76; N, 8.52; S, 19.50%. Found: C, 58.29; H, 2.90; N, 8.30; S, 19.22; Cl, 10.20%. IR: $\nu = 3190–3180$ (NH), 2210 (CN) cm^{-1}. ^1H NMR (DMSO): $\delta = 8.2$ (d, 1H, CH thienyl), 7.5–7.8 (m, 6H: 4ArH's, CH thienyl and CH pyridine), 7.2 (m, 1H, CH thienyl) ppm.

Reaction of 2a–c with Chloroacetonitrile or Chloroacetamide: Formation of *S*-substituted Thiopyridines 3a–c and 5a–c Respectively

To a suspension of compound **2a–c** (20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50 ml), chloroacetonitrile or chloroacetamide (20 mmol) was added. The resulting mixture was heated under reflux for 2 h. The precipitate that formed on cooling was collected and recrystallized from ethanol as pale yellow needles of **3a–c** or **5a–c** respectively.

(3-Cyano-4-phenyl-6-(2′-thienyl)-2-pyridinylthio)-acetonitrile (3a)

Yield: 87%; m.p.: 225°C. Anal. Calcd. for $C_{18}H_{11}N_3S_2$ (333.43): C, 64.84; H, 3.33; N, 12.60; S, 19.23%. Found: C, 64.65; H, 3.15; N, 12.35; S, 19.39%. IR: $\nu = 2220$, 2200 (2CN) cm^{-1}. ^1H NMR (TFA): $\delta = 7.3–8.3$ (m, 9H: 5ArH's, 3CH thienyl and CH pyridine), 4.4 (s, 2H, SCH_2) ppm.

(3-Cyano-4-(*p*-methoxyphenyl)-6-(2′-thienyl)-2-pyridinylthio)acetonitrile (3b)

Yield: 89%; m.p.: 220°C. Anal. Calcd. for $C_{19}H_{13}N_3OS_2$ (363.46): C, 62.79; H, 3.61; N, 11.56; S, 17.64%. Found: C, 62.95; H, 3.82; N, 11.46; S, 17.51%. IR: $\nu = 2220$, 2200 (2CN) cm^{-1}.

4-(*p*-Chlorophenyl)-3-cyano-6-(2′-thienyl)-2-pyridinylthio)acetonitrile (3c)

Yield: 92%; m.p.: 210°C. Anal. Calcd. for $C_{18}H_{10}ClN_3S_2$ (367.89): C, 58.77; H, 2.74; N, 11.42; S, 17.43; Cl, 9.64%. Found: C, 58.69; H, 2.85; N, 11.70; S, 17.50; Cl, 9.43%. IR: = 2220, 2200 (2CN) cm^{-1}.

(3-Cyano-4-phenyl-6-(2′-thienyl)-2-pyridinylthio)-acetamide (5a)

Yield: 95%; m.p.: 228°C. Anal. Calcd. for $C_{18}H_{13}N_3OS_2$ (351.45): C, 61.51; H, 3.73; N, 11.96; S, 18.25%. Found: C, 61.77; H, 3.85; N, 11.68; S, 18.12%. IR: ν = 3450, 3320 (NH_2); 2200 (CN); 1680 (CO) cm^{-1}. ^1H NMR (DMSO): δ = 8.2 (d, 1H, CH thienyl), 7.3–8.3 (m, 10H: 5ArH's, 2CH thienyl, CH pyridine and $CONH_2$), 4.1 (s, 2H, SCH_2) ppm.

(3-Cyano-4-(*p*-methoxyphenyl)-6-(2′-thienyl)-2-pyridinylthio)acetamide (5b)

Yield: 96%; m.p.: 210°C. Anal. Calcd. for $C_{19}H_{15}N_3O_2S_2$ (381.46): C, 59.82; H, 3.96; N, 11.02; S, 16.81%. Found: C, 59.59; H, 4.08; N, 11.00; S, 16.74%. IR: ν = 3450, 3320 (NH_2); 2200 (CN); 1680 (CO) cm^{-1}. ^1H NMR (DMSO): $\delta = 8.2$ (d, 1H, CH thienyl), 7.2–8.0 (m, 9H: 4ArH's, 2CH thienyl, CH pyridine and $CONH_2$), 4.2 (s, 2H, SCH_2), 3.4 (s, 3H, OCH_3) ppm.

(4-(*p*-Chlorophenyl)-3-cyano-6-(2′-thienyl)-2-pyridinylthio)acetamide (5c)

Yield: 95%; m.p.: 222°C. Anal. Calcd. for $C_{18}H_{12}ClN_3OS_2$ (385.90): C, 56.02; H, 3.13; N, 10.89; S, 16.62; Cl, 9.19%. Found: C, 56.32; H, 3.17; N, 10.65; S, 16.57; Cl, 9.10%. IR: ν = 3450, 3320 (NH_2); 2200 (CN); 1680 (CO) cm^{-1}. ^1H NMR (DMSO): δ = 8.2 (d, 1H, CH thienyl), 7.3–8.0 (m, 9H: 4ArH's, 2CH thienyl, CH pyridine and $CONH_2$), 4.0 (s, 2H, SCH_2).

2-Functionalized 3-amino-4-aryl-6-(2′-thienyl)-thieno-[2,3-b]pyridines 4a–c, and 6a–c

Method A

Compounds **3a–c** or **5a–c** (10 mmol) were suspended in sodium ethoxide solution (0.12 g sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give canary yellow crystals of **4a–c** and **6a–c** respectively.

*3-Amino-4-phenyl-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carbonitrile (**4a**).* Yield: 90%; m.p.: 260°C. Anal. Calcd. for $C_{18}H_{11}N_3S_2$ (333.43): C, 64.84; H, 3.33; N, 12.60; S, 19.23%. Found: C, 64.93; H, 3.12; N, 12.89; S, 19.00%. IR: $\nu = 3450, 3350$ (NH_2), 2200 (CN) cm^{-1}.

*3-Amino-4-(*p*-methoxyphenyl)-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carbonitrile (**4b**).* Yield: 92%; m.p.: 225°C. Anal. Calcd. for $C_{19}H_{13}N_3OS_2$ (363.46): C, 62.79; H, 3.61; N, 11.56; S, 17.64%. Found: C, 62.65; H, 3.66; N, 11.71; S, 17.87%. IR: $\nu = 3450, 3350$ (NH_2), 2200 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 7.1–8.1$ (m, 8H:4ArH's, 3CH thienyl and CH pyridine), 5.7 (s, 2H, NH_2), 3.9 (s, 3H, OCH_3) ppm.

*3-Amino-4-(*p*-chlorophenyl)-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carbonitrile (**4c**).* Yield: 89%; m.p.: 261°C. Anal. Calcd. for $C_{18}H_{10}ClN_3S_2$ (367.89): C, 58.77; H, 2.74; N, 11.42; S, 17.43; Cl, 9.64%. Found: C, 58.54; H, 2.67; N, 11.74; S, 17.62; Cl, 9.81%. IR: $\nu = 3450, 3350$ (NH_2), 2200 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 7.2–8.1$ (m, 8H: 4ArH's, 3CH thienyl and CH pyridine), 5.6 (s, 2H, NH_2) ppm. MS: m/z = 367.5 (M^+, 100%), 341 (M^+-CN, 1%), 331 (M^+-Cl, 9%), 298 (M^+-Cl-C_4H_3S, 1.5%).

*3-Amino-4-phenyl-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carboxamide (**6a**).* Yield: 90%; m.p.: 235–8°C. Anal. Calcd. for $C_{18}H_{13}N_3OS_2$ (351.45): C, 61.51; H, 3.73; N, 11.96; S, 18.25%. Found: C, 61.61; H, 3.94; N, 11.75; S, 18.08%. IR: $\nu = 3480, 3300, 3150$ (NH_2), 1640 (CO) cm^{-1}.

*3-Amino-4-(*p*-methoxyphenyl)-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carboxamide (**6b**).* Yield: 95%; m.p.: 231°C. Anal. Calcd. for $C_{19}H_{15}N_3O_2S_2$ (381.46): C, 59.82; H, 3.96; N, 11.02; S, 16.81%. Found: C, 59.65; H, 4.06; N, 11.32; S, 16.79%. IR: $\nu = 3480, 3300, 3150$ (NH_2), 1640 (CO) cm^{-1}. ^1H NMR (DMSO): $\delta = 7.1–8.1$ (m, 10H: 4ArH's, 3CH thienyl, CH pyridine and $CONH_2$), 5.9 (s, 2H, NH_2), 3.5 (s, 3H, OCH_3) ppm.

*3-Amino-4-(*p*-chlorophenyl)-6-(2′-thienyl)-thieno[2,3-b]pyridine-2-carboxamide (**6c**).* Yield: 95%; m.p.: 240–243°C. Anal. Calcd. for

$C_{18}H_{12}ClN_3OS_2$ (385.90): C, 56.02; H, 3.13; N, 10.89; S, 16.62; Cl, 9.19%. Found: C, 56.01; H, 3.14; N, 10.95; S, 16.77; Cl, 9.12%. IR: ν = 3480, 3300, 3150 (NH_2), 1640 (CO) cm^{-1}. ^1H NMR (DMSO): δ = 8.0 (d, 1H, CH thienyl), 7.5–7.8 (m, 6H: 4ArH's, CH thienyl and CH pyridine), 7.3 (m, 3H, CH thienyl and $CONH_2$), 5.9 (s, 2H, NH_2) ppm.

Method B

To a suspension of compound **2a–c** (10 mmol) in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), chloroacetonitrile or chloroacetamide (10 mmol) was added. The resulting mixture was refluxed for 20 min. The formed precipitate was collected and recrystallized from ethanol-chloroform mixture to give compounds **4a–c** and **6a–c** respectively (yield; 76–83%). These products were identical in all aspects to those described in method A.

4-Amino-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine (7)

Compound **4a** (0.66 g, 0.002 mmol) in formamide (10 ml) was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give white crystals of **7**. Yield: 0.62 g (87%); m.p.: 270°C. Anal. Calcd. for $C_{19}H_{12}N_4S_2$ (360.46): C, 63.31; H, 3.36; N, 15.54; S, 17.79%. Found: C, 63.45; H, 3.14; N, 15.72; S, 17.59%. IR: ν = 3190, 3100 (NH_2), 1640 (C=N) cm^{-1}. MS: m/z = 360.48 (M^+, 91%), 359 (M^+-H, 100%).

2,4-Dithioxo-9-phenyl-1,2,3,4-tetrahydro-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (8)

A mixture of compound **4a** (0.66 g, 0.002 mmol) and carbon disulfide (1 ml) in pyridine (10 ml) was heated under reflux on a water bath for 6 h. The solid that formed while hot was collected and recrystallized from DMF to give orange crystals of **8**. Yield: 0.71 g (88%); m.p.: >360°C. Anal. Calcd. for $C_{19}H_{11}N_3S_4$ (409.57): C, 55.72; H, 2.71; N, 10.26; S, 31.31%. Found: C, 55.88; H, 2.82; N, 10.17; S, 31.00%. IR: ν = 3350, 3100 (2NH) cm^{-1}. MS: m/z = 410.6 (M^++1, 21%), 409.7 (M^+, 8%), 408.7 (M^+-H, 100%), 375.7 (M^+-H–SH, 14%), 350.8 (M^+-1-HNCS, 12%).

2,4-Dimethylthio-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine (9a)

To a solution of compound **8** (0.81 g, 0.002 mmol) in an ethanolic sodium hydroxide solution 4% (10 ml, 0.01 mmol), methyl iodide (0.4 ml,

0.006 mmol) was added. The resulting mixture was refluxed for 2 h and then left to cool. The precipitated solid was collected and recrystallized from ethanol to give white needles of **9a**. Yield: 0.85 g (97%); m.p.: 269°C. Anal. Calcd. for $C_{21}H_{15}N_3S_4$ (437.63): C, 57.64; H, 3.45; N, 9.60; S, 29.31%. Found: C, 57.82; H, 3.75; N, 9.71; S, 29.56%. IR: $\nu = 1600$ (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.2–7.8$ (m, 9H: 5ArH's, 3CH thienyl and CH pyridine), 2.7 (s, 3H, CH_3), 2.0 (s, 3H, CH_3) ppm.

2,4-Diethoxycarbonylmethylthio-9-phenyl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (9b)

To a suspension of **8** (0.81 g, 0.002 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50 ml), ethyl chloroacetate (0.5 ml, 0.004 mmol) was added. The resulting mixture was refluxed for 2 h. The precipitate that formed after cooling was collected and recrystallized from ethanol to give white needles of **9b**. Yield: 1.0 g (90%); m.p.: 121°C. Anal. Calcd. for $C_{27}H_{23}N_3O_4S_4$ (581.75): C, 55.74; H, 3.98; N, 7.22; S, 22.05%. Found: C, 55.97; H, 4.00; N, 9.23; S, 22.16%. IR: $\nu =$ 1730 (CO), 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): d = 7.1–7.8 (m, 9H: 5ArH's, 3CH thienyl and CH pyridine), 4.0–4.3 (m, 8H, $2XSCH_2$ and $2XOCH_2$), 1.2–1.4 (m, 6H, $2XCH_3$) ppm.

4-Imino-3,9-diphenyl-1,2,3,4-tetrahydro-7-(2′-thienyl)-2-thioxopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (10)

A mixture of compound **4a** (0.66 g, 0.002 mmol) and phenyl isothiocyanate (0.25 ml, 0.002 mmol) in pyridine (10 ml) was gently heated under reflux for 6 h. The solid that formed on cooling was collected and recrystallized from acetic acid to give orange crystals of **10**. Yield: 0.88 g (94%); m.p.: 272°C. Anal. Calcd. for $C_{25}H_{16}N_4S_3$ (468.61): C, 64.07; H, 3.44; N, 11.96; S, 20.53%. Found: C, 64.35; H, 3.29; N, 11.80; S, 20.27%. IR: $\nu = 3380, 3200$ (2NH) cm^{-1}. MS: m/z = 468 (M^+, 100%), 435 (M^+-SH, 11%), 410 (M^+-1-HNCS, 49%), 77 ($C_6H_5^+$, 85%).

3-Amino-2-(4,5-dihydroimidazol-2-yl)-4-phenyl-6-(2′-thienyl)-thieno[2,3-b]pyridine (11)

To a suspension of compound **4a** (1.6 g, 0.005 mmol) in ethylene diamine (5 ml), carbon disulfide (2 ml) was added dropwise. The reaction mixture was heated on a water bath for 2 h and then triturated with ethanol (10 ml). The solid that formed was collected and recrystallized from ethanol-chloroform mixture to give golden yellow crystals of **11**. Yield: 1.6 g (88%); m.p.: 190°C. Anal. Calcd. for $C_{20}H_{16}N_4S_2$ (376.5): C,

63.80; H, 4.28; N, 14.88; S, 17.03%. Found: C, 63.91; H, 4.43; N, 14.56; S, 17.00%. IR: $\nu = 3400$, 3250 (NH_2), 3100 (NH) cm^{-1}. ^1H NMR (DMSO)): $\delta = 7.7$–8.2 (m, 8H: 5ArH's, 2CH thienyl and CH pyridine), 7.3 (m, 1H, CH thienyl), 6.0 (br, 2H, NH_2), 3.6 (s, 4H, $2XCH_2$) ppm.

3-Amino-4-phenyl-6-(2′-thienyl)-2-(1*H*-tetrazol-2′-yl)-thieno[2,3-b]pyridine (12)

A mixture of compound **4a** (1.3 g, 0.004 mmol), sodium azide (0.4 g, 0.006 mmol), and ammonium chloride (0.32 g, 0.006 mmol) in DMF (15 ml) was heated on a water bath for 5 h. The reaction was cooled, diluted with water, and acidified with dilute acetic acid. The solid that formed was collected and crystallized from ethanol to give golden yellow crystals of **12**. Yield: 1.35 g (92%); m.p.: 279°C. Anal. Calcd. for $C_{18}H_{12}N_6S_2$ (376.46): C, 57.43; H, 3.21; N, 22.32; S, 17.04%. Found: C, 57.49; H, 3.18; N, 22.40; S, 17.32%. IR: $\nu = 3490$, 3370 (NH_2), 3250 (NH) cm^{-1}.

7-Phenyl-9-(2′-thienyl)-2,3-dihydroimidazolo[1″,2″-c]-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (13)

Compound **11** (0.75 g, 0.002 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from pyridine to give pale yellow needles of **13**. Yield: 0.7 g (94%); m.p.: 307 C. Anal. Calcd. for $C_{21}H_{14}N_4S_2$ (386.49): C, 65.26; H, 3.65; N, 14.50; S, 16.30%. Found: C, 65.53; H, 3.88; N, 14.42; S, 16.30%. IR: $\nu = 1640$ (C=N) cm^{-1}. ^1H NMR (TFA): $\delta = 8.8$ (s, 1H, CH pyrimidine), 7.5–8.4 (m, 9H: 5ArH's, 3CH thienyl and CH pyridine), 5.1 (br, 2H, CH_2), 4.5 (br, 2H, CH_2) ppm.

5-(*p*-Chlorophenyl)-7-phenyl-9-(2′-thienyl)-2,3,5,6-tetrahydroimidazolo[1″,2″-c]pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine (14)

To a mixture of compound **11** (0.75 g, 0.002 mmol) and *p*-chlorobenzaldehyde (0.28 g, 0.002 mmol) in ethanol (15 ml), few drops of piperidine were added. The reaction mixture was heated under reflux for 4 h. The solid that formed on cooling was collected and recrystallized from dioxane to give yellow crystals of **14**. Yield: 0.9 g (90%); m.p.: 286°C. Anal. Calcd. for $C_{27}H_{19}N_4S_2Cl$ (499.07): C, 64.98; H, 3.84; N, 11.23; S, 12.85; Cl, 7.11%. Found: C, 64.87; H, 3.58; N, 11.11; S, 12.96; Cl, 7.06%. IR: $\nu = 3330$ (NH) cm^{-1}. ^1H NMR (TFA): $\delta = 8.8$ (m, 1H, CH thienyl), 7.3–8.4 (m, 12H: 9ArH's, 2CH thienyl and CH pyridine), 6.1 (s, 1H, CH), 4.2 (s, 2H, CH_2), 3.7 (s, 2H, CH_2) ppm.

7-Phenyl-9-(2′-thienyl)-5-thioxo-2,3,5,6-tetrahydro-imidazolo[1″,2″-c]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (15)

A mixture of compound **11** (0.75 g, 0.002 mmol) and carbon disulfide (1 ml) in pyridine (10 ml) was heated under reflux on a water bath for 8 h. The solid that formed while hot was collected and recrystallized from DMF to give orange crystals of **15**. Yield: 0.78 g (93%); m.p.: >360°C. Anal. Calcd. for $C_{21}H_{14}N_4S_3$ (418.56): C, 60.26; H, 3.37; N, 13.39; S, 22.94%. Found: C, 60.11; H, 3.42; N, 13.59; S, 22.56%. IR: ν = 3400 (NH), 1640 (C=N) cm^{-1}. MS: m/z = 418 (M^+, 100%).

7-Phenyl-9-(2′-thienyl)-2,3-dihydroimidazolo[1″,2″-c]-pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine (16)

Sodium nitrite solution 10% (5 ml) was added to a solution of **11** (0.75 g, 0.002 mmol) in concentrated sulfuric acid (5 ml) and acetic acid (5 ml) at 0°C during 5 min. with stirring. The reaction mixture was allowed to stand at room temperature for 30 min. The solid that precipitated on dilution with water was collected and crystallized from dioxane to give white needles of **16**. Yield: 0.65 g (87%); m.p.: 282°C. Anal. Calcd. for $C_{20}H_{13}N_5S_2$ (387.48): C, 61.99; H, 3.68; N, 18.07; S, 16.55%. Found: C, 61.71; H, 3.45; N, 18.30; S, 16.24%. IR: ν = 1640 (C=N) cm^{-1}.

7-Phenyl-9-(2′-thienyl)-tetrazolo[1″,2″-c]pyrido-[3′,2′:4,5]thieno[2,3-e]pyrimidine (17)

Compound **12** (0.75 g, 0.002 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 3 h and then left to cool. The precipitate that formed was collected and recrystallized from dioxane to give pale yellow needles of **17**.Yield: 0.68 g (89%); m.p.: 222°C. Anal. Calcd. for $C_{19}H_{10}N_6S_2$ (386.46): C, 59.05; H, 2.61; N, 21.75; S, 16.59%. Found: C, 59.21; H, 2.25; N, 21.43; S, 16.40%. IR: ν = 1600 (C=N) cm^{-1}.

7-Phenyl-9-(2′-thienyl)-tetrazolo[1″,2″-c]pyrido-[3′,2′:4,5]thieno[2,3-e]pyrimidine-5(6*H*)-thione (18)

A mixture of compound **12** (0.75 g, 0.002 mmol) and carbon disulfide (4 ml) in pyridine (15 ml) was heated under reflux on a water bath for 12 h. The solid that formed while hot was collected and recrystallized from DMF to give yellow crystals of **18**. Yield: 0.70 g (84%); m.p.: 317°C. Anal. Calcd. for $C_{19}H_{10}N_6S_3$ (418.52): C, 54.53; H, 2.41; N, 20.08; S, 23.00%. Found: C, 54.22; H, 2.25; N, 20.11; S, 22.70%. IR: ν = 3330 (NH), 1620 (C=N) cm^{-1}.

4-Chloro-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno-[3,2-d][1,2,3]triazine (19)

To a chilled solution of compound **4a** (1.7 g, 0.005 mmol) in a mixture of acetic acid (10 ml) and concentrated hydrochloric acid (7 ml), a sodium nitrite solution 10% (4 ml, 0.006 mmol) was added with stirring during 5 min. The stirring was continued at 5°C for 3 h. The formed preceiptate was collected and crystallized from ethanol-chloroform mixture to give white plates of **19**. Yield: 1.7 g (89%); m.p.: 236°C; Anal. Calcd. for $C_{18}H_9ClN_4S_2$ (380.88): C, 56.76; H, 2.38; N, 14.71; S, 16.84; Cl, 9.31%. Found: C, 56.90; H, 2.22; N, 14.91; S, 16.87; Cl, 9.10%. IR: $\nu = 1600$ (C=N) cm^{-1}.

4-Hydrazino-9-phenyl-7-(2′-thienyl)-pyrido[3′,2′:4,5]-thieno[3,2-d][1,2,3]triazine (20)

A mixture of **19** (1.5 g, 0.004 mmol) and hydrazine hydrate 99% (4.0 ml in ethanol (35 ml), was heated under reflux for 4 h. The solid that formed on cooling was collected and recrystallized from dioxane to give pale yellow crystals of **20**. Yield: 1.35 g (91%); m.p.: 154°C. Anal. Calcd. for $C_{18}H_{12}N_6S_2$ (376.46): C, 57.43; H, 3.21; N, 22.32; S, 17.04%. Found: C, 57.28; H, 3.19; N, 22.13; S, 17.30%. IR: $\nu = 3320–3200$ ($NHNH_2$) cm^{-1}.

4-(3′,5′-dimethylpyrazol-1′-yl)-9-Phenyl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine (21)

A mixture of compound **20** (0.75 g, 0.002 mmol) and acetylacetone (2 ml, 0.02 mmol) in ethanol (15 ml) was heated under reflux for 5 h. The crystalline precipitate that formed while hot was collected and recrystallized from ethanol-chloroform as greenish crystals of **21**. Yield: 0.8 g (91%); m.p.: 310°C. Anal. Calcd. for $C_{23}H_{16}N_6S_2$ (440.55): C, 62.71; H, 3.66; N, 19.08; S, 14.56%. Found: C, 62.35; H, 3.32; N, 19.01; S, 14.35%. IR: $\nu = 1600$ (C=N) cm^{-1}. ^1H NMR (TFA): $\delta = 7.5–8.5$ (m, 9H: 5 ArH's, 3CH thienyl and CH pyridine), 6.5 (s, 1H, CH pyrazole), 2.9 (s, 3H, CH_3), 2.5 (s, 3H, CH_3) ppm.

4-Oxo-9-phenyl-1,2,3,4-tetrahydro-7-(2′-thienyl)-2-thioxopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (22)

A mixture of **6a** (1.0 g, 3 mmol) and carbon disulphide (4 ml) in dry pyridine (30 ml) was heated on a water bath for 48 h. The solid thus formed while hot was collected and recrystallized from DMF as yellow

crystals of **22**. Yield: 88%; m.p.: >360°C. Anal. Calcd. for $C_{19}H_{11}N_3OS_3$ (393.51): C, 57.99; H, 2.82; N, 10.68; S, 24.44%. Found: C, 58.04; H, 2.73; N, 10.39; S, 24.55%. IR: υ = 3350–3100 (NH), 1680 (C=O) cm^{-1}.

Reaction of 22 with Halo Compounds; Formation of Compounds 23a,b: General Procedure

A solution of compound **22** (0.39 g, 1 mmol) in DMF (7 ml) was stirred for a while with potassium carbonate (0.3 g, 4 mmol) and then alkylating agent (1 mmol) was added. The reaction mixture was heated on a water bath for **1** h and then diluted with water. The precipitate that formed was filtered off, dried and crystallized from ethanol as pale yellow crystals of **23a** or **23b**.

a) 3-Ethyl-2-ethylthio-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3 **H** *)-one (23a)*

Obtained by using ethyl iodide. Yield: 92%; m.p.: 190°C. Anal. Calcd. for $C_{23}H_{19}N_3OS_3$ (450.22): C, 61.36; H, 4.25; N, 9.47; S, 21.37%. Found: C, 61.22; H, 4.16; N, 9.39; S, 21.57%. IR: υ = 1670 (C=O) cm^{-1}. ^{1}H NMR (TFA): δ = 7.7–8.4 (m, 8H: 5ArH's, 2CH thienyl and CH pyridine), 7.6 (m, 1H, CH thienyl), 4.4 (q, 2H, NCH_2), 2.8 (q, 2H, SCH_2), 2.4–2.7 (t, 6H, 2xCH_3) ppm.

b) 3-Ethoxycarbonylmethyl-2-ethoxycarbonylmethythio-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(1 **H**,*3* **H** *)-one (23b)*

Obtained by using ethyl chloroacetate. Yield: 90%; m.p.: 151°C. Anal. Calcd. for $C_{27}H_{23}N_3O_5S_3$ (479.60): C, 57.60; H, 3.57; N, 8.76; S, 20.06%. Found: C, 57.79; H, 3.54; N, 8.91; S, 20.32%. IR: υ = 1720 (C=O, ester), 1670 (C=O, pyrimidinone) cm^{-1}. ^{1}H NMR (TFA): δ = 8.2–8.5 (m, 3H: 2CH thienyl and CH pyridine), 7.8–8.1 (m, 5H, ArH), 7.6 (m, 1H, CH thienyl), 5.6 (s, 2H, NCH_2), 4.4–4.7 (q, 4H, 2xOCH_2), 4.1 (s, 2H, SCH_2), 1.4–1.7 (q, 6H, 2 × CH_3) ppm.

9-Aryl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-4(3*H*)-ones (24b,c)

A mixture of compounds **6b**,**c** (5 mmol) and triethyl orthoformate (4 ml) in acetic anhydride (20 ml) was refluxed for 4 h. The solid that formed on cooling was filtered off and recrystallized from ethanol-chloroform mixture as white crystals of **24b**,**c**.

Compound 24b

Yield: 80%; m.p.: 340°C. Anal. Calcd. for $C_{20}H_{13}N_3O_2S_2$ (391.47): C, 61.36; H, 3.35; N, 10.73; S, 16.38%. Found: C, 61.11; H, 3.53; N, 10.61; S, 16.22%. IR: υ = 3200–2000 (NH), 1650 (C=O) cm^{-1}. ^1H NMR (TFA): δ = 9.1 (s, 1H, CH pyrimidine), 8.1–8.4 (m, 3H, 2CH thienyl and CH pyridine), 7.8–8.0 (d, 2H, ArH's), 7.3–7.7 (m, 3H: 2ArH's and CH thienyl), 4.1 (s, 3H, OCH_3) ppm.

Compound 24c

Yield: 80%; m.p.: 350°C. Anal. Calcd. for $C_{19}H_{10}ClN_3OS_2$ (395.89): C, 57.64; H, 2.55; N, 10.61; S, 16.20%. Found: C, 57.89; H, 2.77; N, 10.90; S, 16.53%. IR: υ = 3200–2000 (NH), 1650 (C=O) cm^{-1}.

9-Aryl-7-(2′-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]-[1,2,3]triazine-4(3*H*)-ones (25a–c)

To a cold solution of **6a–c** (10 mmol) in conc. H_2SO_4 (5 ml) and glacial acetic acid (20 ml), sodium nitrite solution 10% (7.7 ml, 11 mmol) was added dropwise with stirring during 5 min at room temperature. The formed precipitate was collected dried in air and crystallized from ethanol-chloroform mixture to give compounds **25a–c**.

Compound 25a

Obtained from **6a**. Yield: 93%; m.p.: >360°C. Anal. Calcd. for $C_{18}H_{10}N_4OS_2$ (362.43): C, 59.65; H, 2.78; N, 15.46; S, 17.69%. Found: C, 59.74; H, 2.76; N, 15.41; S, 17.81%. IR: υ = 3200 (NH), 1650 (C=O) cm^{-1}.

Compound 25b

Obtained from **6b**. Yield: 83%; m.p.: 303°C. Anal. Calcd. for $C_{19}H_{12}N_4O_2S_2$ (392.46): C, 58.15; H, 3.08; N, 14.28; S, 16.34%. Found: C, 58.11; H, 2.98; N, 13.96; S, 16.05%. IR: υ = 3200 (NH), 1650 (C=O) cm^{-1}. ^1H NMR (TFA): δ = 8.1–8.4 (m, 3H, 2CH thienyl and CH pyridine), 7.8–8.0 (d, 2H, ArH's), 7.3–7.7 (m, 3H: 2ArH's and CH thienyl), 4.0 (s, 3H, OCH_3) ppm.

Compound 25c

Obtained from **6c**. Yield: 87%; m.p.: 235°C. Anal. Calcd. for $C_{18}H_9ClN_4OS_2$ (369.88): C, 54.47; H, 2.29; N, 14.12; S, 16.16; Cl, 8.93%. Found: C, 54.52; H, 2.01; N, 14.30; S, 16.33; Cl, 8.71%. IR: υ = 3200 (NH), 1650 (C=O) cm^{-1}.

Alkylation of 9-Phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3*H*)-one (25a); Formation of 26a–c

A solution of triazinone derivative **25a** (0.36 g, 1 mmol) in DMF (7 ml) was stirred for a while with potassium carbonate (0.3 g) and then alkylating agent (1 mmol) in DMF (7 ml) was added. The reaction mixture was stirred for 2 h at room temperature and then diluted with water. The formed precipitate was filtered off, dried in air and crystallized from the proper solvent to give **26a–c**.

*a) 3-*p*-Bromophenacyl-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3H)-one (26a)*

Obtained from **25a** and *p*-bromophenacyl bromide (ethanol-chloroform). Yield: 81%; m.p.: 279°C. Anal. Calcd. for $C_{26}H_{15}BrN_4O_2S_2$ (559.46): C, 55.82; H, 2.70; N, 10.01; S, 11.46%. Found: C, 55.67; H, 2.65; N, 10.30; S, 11.70%. IR: $\upsilon = 1670$ (2C=O) cm^{-1}.

b) 3-Ethoxycarbonylmethyl-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3H)-one (26b)

Obtained from **25a** and ethyl chloroacetate (ethanol). Yield: 88%; m.p.: 245°C. Anal. Calcd. for $C_{22}H_{16}N_4O_3S_2$ (448.53): C, 58.91; H, 3.60; N, 12.49; S, 14.30%. Found: C, 58.88; H, 3.57; N, 12.47; S, 14.40%. IR: $\upsilon =$ 1720 (C=O, ester), 1670 (C=O, triazinone) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta =$ 7.8–8.2 (m, 8H: 5ArH's, 2CH thienyl and CH pyridine), 7.4–7.5 (t, H, CH thienyl), 5.4 (s, 2H, SCH_2), 4.3–4.5 (q, 2H, OCH_2), 1.3–1.5 (t, 3H, CH_3) ppm.

c) 3-Carbamoylmethyl-9-phenyl-7-(2′-thienyl)-pyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3H)-one (26c)

Obtained from **25a** and chloroacetamide (ethanol). Yield: 83%; m.p.: 351°C. Anal. Calcd. for $C_{20}H_{13}N_5O_2S_2$ (419.49): C, 57.27; H, 3.12; N, 16.70; S, 15.29%. Found: C, 54.42; H, 3.01; N, 16.94; S, 15.12%. IR: $\upsilon =$ 3400, 3300 cm^{-1} for (NH_2), 1680 (C=O, amide), 1670 (C=O, triazinone) cm^{-1}. ^1H NMR (DMSOF: 8 = 7.5–8.1 (m, gH; ArHs, 2CH thienyl and CH pyridine); 7.2 (br, 2H, $CONH_2$), 3.4 (S, 2H, NCH_2).

REFERENCES

[1] Z. Shraideh and A.-K. Sallal, *Biomed. Lett*., **54,** 233 (1997).

[2] J. Bompart, L. Giral, G. Malicorne, and M. Puygrenier, *Eur. J. Med. Chem*., **22,** 139 (1987).

[3] M. E. Schnute, M. M. Cudahy, and A. Scott, PCT Int. Appl. WO 00, 53,610 (2000): *C. A*. **133,** 222706g (2000).

[4] I. Adachi and Y. Hiramatsu, Jpn. Pat. 03,52,890 (1991): *C. A.*, **115,** 71573 (1991).
[5] S. Furuya, N. Takeyru, and H. Matsumoto, Jpn. Pat. 09,169,766 (1997): *C. A.*, **127,** 176416 (1997).
[6] S. Furuya, N. Choh, N. Suzuki, and T. Imada, PCT Int. Appl. WO 000,00,493 (2000): *C. A.*, **132,** 64179 (2000).
[7] C. G. Dave, P. R. Shah, K. C. Dave, and V. J. Patel, *J. Indian Chem. Soc.*, **66,** 48 (1989).
[8] E. Bousquent, G. Romero, F. Guerrera, A. Caruso, and M. A. Roxas, *Farmaco Ed. Sci.*, **40,** 869 (1985).
[9] S. Leistner, G. Wagener, M. Guestscharo, and E. Glusa, *Pharmazie*, **41,** 54 (1986).
[10] G. Wagner, S. Leistner, H. Vieweg, U. Krasselt, and J. Prantz, *Pharmazie*, **48,** 514 (1993).
[11] R. D. Youssefyeh, R. E. Brown, J. Wilson, et al., *J. Med. Chem.*, **27,** 1639 (1984).
[12] E. A. Bakhite, A. E. Abdel-Rahman, O. S. Mohamed, and E. A. Thabet, *Pharmazie*, **55,** 577 (2000).
[13] A. E. Abdel-Rahman, E. A. Bakhite, O. S. Mohamed, and E. A. Thabet, *Phosphorus, Sulfur, and Silicon*, **166,** 149 (2000).
[14] A. E. Abdel-Rahman, E. A. Bakhite, and E. A. Al-Taifi, *J. Chin. Chem. Soc.*, **49,** 223 (2002).