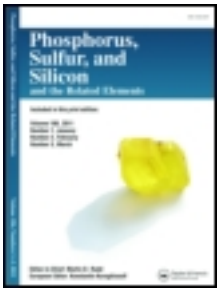

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Acetoacetanilides in Heterocyclic Synthesis, Part 1: An Expeditious Synthesis of Thienopyridines and Other Fused Derivatives

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Acetoacetanilides in Heterocyclic Synthesis, Part 1: An Expeditious Synthesis of Thienopyridines and Other Fused Derivatives

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*3-Oxo-N-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **1** reacts with arylidinecyanothioacetamide in refluxing ethanolic TEA to give the pyridinethione **2** rather than thiopyrane **4**. Compound **2** reacts with α-haloketones to give the s-alkylated derivatives **7a–e**. Compound **7a–e** undergoes cyclization into thieno[2,3-b]pyridine derivatives **8a–e**. The saponification of **8a** gives the amino acid **9**, which affords **10** when refluxed in Ac_2O. The treatment of **10** with $NH_4OAc/AcOH$ gives **11**. Compound **II** is also obtained when **8e** is refluxed in Ac_2O. The reaction of **8a** with hydrazine hydrate gives **12** and with formamide gives **13**. Compound **13** also is obtained from the reaction of **8e** with triethylorthoformate. The acetylation of **8a** with Ac_2O gives the amide derivative **14**, which, on treatment with aromatic amines, affords **15a–c**. Compounds **15a–c** are cyclized with H_2SO_4 to **16a–c**. Compound **16** is obtained also from the acetylation of compound **8c,d** by Ac_2O. Reactions of compound **8e** with CS_2 in refluxing dioxane afford **17**. The diazotization and self-coupling of **8e** give the pyridothienotriazine **18**. Finally, the chloronation of compound **13** with $POCl_3$ affords the chloride derivative **19**.*

Keywords Pyridinethione; pyridothienooxazine; pyridothienopyrimidine; pyridothienotriazine; thieno[2,3-*b*]pyridines

INTRODUCTION

No doubt that thienopyridine is an interesting class of heterocycles, and their chemistry has recently received considerable attention, especially because of their potential utility as antibacterial,[1–9] antihypertensive.[10] Some fused theinopyridines

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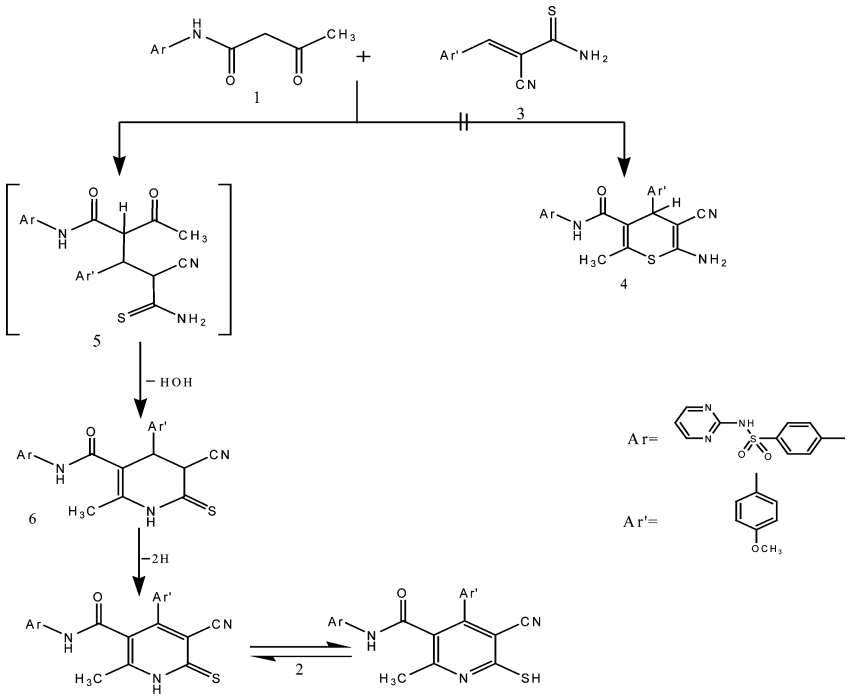
such as pyridothienopyrimidine derivatives have applications as analgesics,[11] antipyretics,[12] and antiinflammatories.[13] Also, the pyridothienotriazine moities are known to exhibit anaphylatic,[14] and antiallergic activity. In continuation of our efforts on the chemistry of pyridinethione and its derivatives,[15] we report here a synthesis of new thieno[2,3-*b*]pyrimidine and other fused derivatives using acetoacetanilide derivative **1** as a starting material.

RESULTS AND DISCUSSION

It has been found that 3-oxo-N-{4-[(pyrimidin-2-ylamino)sulfonyl] phenyl} butanamide **1** (prepared by treating an aniline derivative with ethyl acetoacetate as has been described in the literature[16]) readily reacts with arylidinecyanothioacetamide in refluxing ethanol containing a catalytic amount of triethylamine to yield a product that may be structure **2** or its isomer **4**. Establishing the exact structure of the reaction product as structure **2** rather than **4** based on the spectral data. Thus, the ^{1}H NMR spectrum revealed the presence of a singlet signal at $\delta = 8.4$ and 10.6 ppm assigned to 2NH groups and no signal at range $\delta = 4$–5 ppm assigned for the thiopyrane CH-4. So the pyridinethione **2** is considered to be only the reaction product. Also, the mass spectrum of **2** is compatible with the molecular ion peak m/z = 532 (M^{+1}). Compound **2** is assumed to proceed via an initial addition of the active methylene moiety in **1** to the activated double bond in **3**, thus forming the acyclic Michael adduct **5**, which then cyclized to **6** by a loss of water and aromatized by a loss of hydrogen to the final product **2** (Scheme 1).

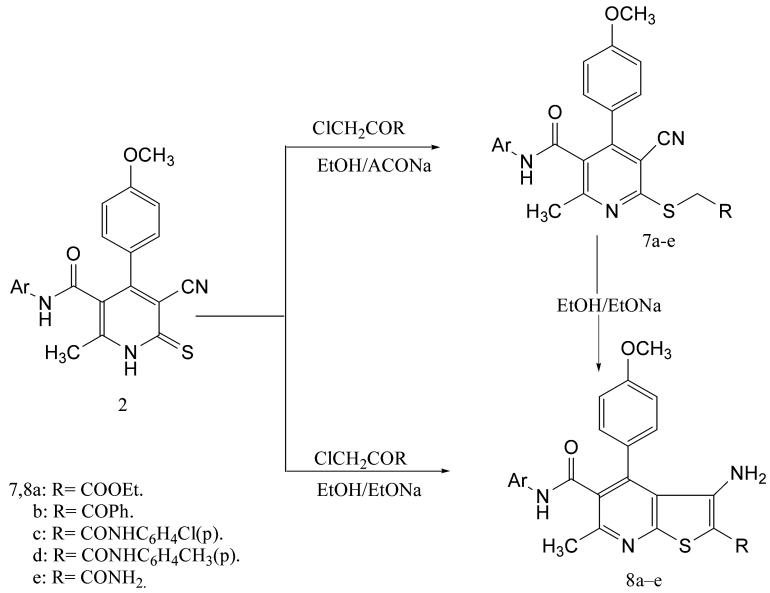
The pyridinethione **2** reacted with α-haloketones in ethanol containing a few grams of sodium acetate to afford the S-alkylated derivatives **7a–e**. The structure of compounds **7a–e** has been confirmed as the correct one based on its spectral data. Thus, the IR spectrum of compound **7a** as an example exhibited the presence of the absorption band of CN function group at γ 2220 cm^{-1}; the ^{1}H NMR spectrum of compound **7a** revealed the appearance of CH_2 protons at $\delta = 4.0$ ppm in addition to the other protons assigned in compound **2**. Also, the mass spectrum of compound **7a** showed the molecular ion peak M^+ at m/z = 618 (36%). Compounds **7a–e** underwent cyclization into thienopyridine derivatives **8a–e** upon treatment with ethanolic sodium ethoxide. The IR spectra of compounds **8a–e** exhibited the disappearance of the absorption band due to the CN function group and the appearance of absorption bands due to the NH_2 function group at γ 3450–3300 cm^{-1}. The ^{1}H NMR spectrum of compound **8a** revealed the disappearance of the protons assigned to the methylene group at $\delta = 4.0$ ppm and revealed the presence



SCHEME 1

of a signal of two protons as a singlet at $\delta = 8.1$ ppm assignable to NH_2 group, beside the protons in their proper positions. A solid evidence for the structure of compounds **8a–e**. Structure **8a–e** has been confirmed as correct one by its synthesis via a reaction of 2 with α-haloketones in boiling ethanolic sodium ethoxide solution (m.p., m.m.p., TLC) (Scheme 2).

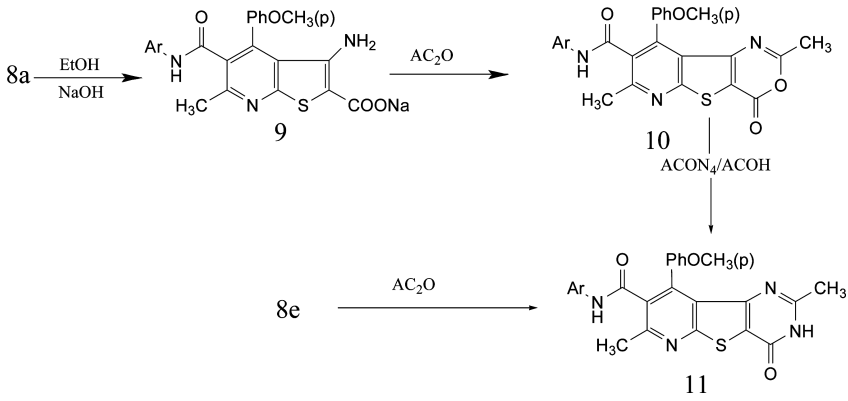
The reactivity of β-amino ester derivative **8a** toward some electrophilic reagents has been studied. Thus, the saponification of **8a** using alcoholic sodium hydroxide yielded the sodium salt of the β-amino acid **9**, which gave the pyridothienooxazine **10** when refluxed in acetic anhydride. The assignment of structure **10** as the reaction product based on its compatible spectroscopic data. Thus, the IR spectrum showed the absence of any absorption bands that may by attributed to NH_2 function group; its mass spectrum revealed a molecular ion peak at m/z (40%) = 614 ($615M^{+1}$) (25%) corresponding to the molecular formula $C_{29}H_{22}N_6O_6S_2$. Moreover, Its ^1H NMR spectrum showed two singlet signals at δ1.2 and 1.8 ppm assigned to $2CH_3$. The treatment of **10** with ammonium acetate in boiling acetic acid led to the formation of



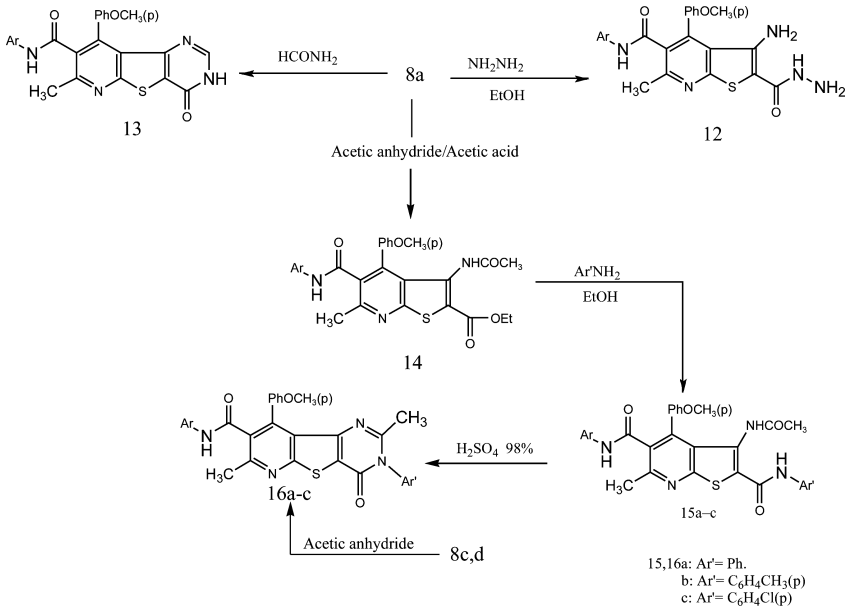
SCHEME 2

pyridothienopyrimidine **11**. Compound **11** can be prepared by refluxing compound **8e** in acetic anhydride (Scheme 3).

Also, **8a** reacted with hydrazine hydrate to afford the hydrazide derivative **12**. The hydrazide **12** was compatible bases on the correct spectroscopic data (IR and ^{1}H NMR). In contrast to this behavior, when compound **8a** was refluxed in formamide solution afforded the expected



SCHEME 3

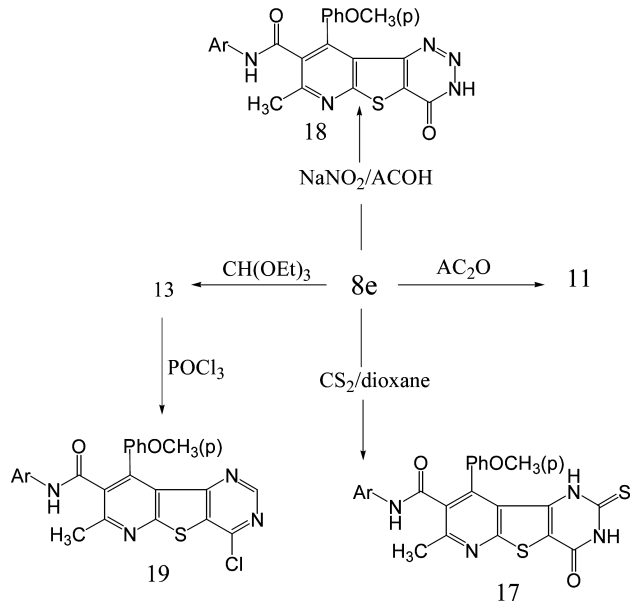


SCHEME 4

pyridothienopyrimidine derivative **13**. On the other hand, the acetylation of **8a** with a mixture of acetic anhydride and glacial acetic acid yielded the acetamide derivative **14**, which on treatment with aromatic amines afforded **15a–c**.

Compounds **15a–c** when treated with 98% sulfuric acid afforded pyridothienopyrimidines **16a–c**. Compounds **16b**,**c** were also obtained by the direct acetylation of compound **8c**,**d** with acetic anhydride (m.p., m.m.p., and TLC) as compounds **16b**,**c** (Scheme 4).

Our investigation extended to include the reactivity of the amino amide derivative **8e** toward some electrophilic reagents. So, the acetylation of compound **8e** with acetic anhydride gave compound **11**, which was identified by (m.p., m.m.p., TLC, and spectroscopic data). The treatment of **8e** with carbon disulfide in boiling dioxane solution afforded the corresponding reaction product **17**. This compound was confirmed by IR, ^{1}H NMR, and elemental analysis). The diazotization and self-coupling of the amino amide derivative **8e** with sodium nitrite and HCl gave the pyrido[3′,2′:4,5]thieno[3,2-*d*]triazine derivative **18**. The structure of compound **18** was confirmed by spectral data. The IR spectrum of **18** showed the absence of any absorption bands that may by attributed to the NH_2 function group. Moreover, the ^{1}H NMR spectrum of **18** revealed the disappearance of the signal due to NH_2



SCHEME 5

protons. When compound **8e** reacts with triethylorthoformate in glacial acetic acid afforded **13**, which was obtained earlier from the treatment of **8a** with formamide. The authentic sample of compound **13** was identified by m.p., m.m.p., TLC, and spectral data. The chloronation of compound **13** with phosphorus oxytrichloride afforded the chloride derivative **19** (Scheme 5).

Conclusion

The importance of the synthesized compounds as an intermediate for the synthesis of biologically active diaza and folic acid ring systems.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp apparatus; IR spectra were recorded on Schimadzu 470 spectrophotometer in potassium bromide discs; ^{1}H NMR spectra were recorded on a Varian EM-390 (90 Mhz) spectrophotometer using TMS as internal standard; mass spectrometer MS 30(AEL)at 70ev. analytical data were obtained from the Microanalytical Data Center at Cairo University, Giza, Egypt.

3-Oxo-N-{4-[(pyrimidin-2-ylamino)sulphonayl]phenyl}-butanamide (1)

Ethylacetoacetate (2.6 mL, 20.0 mmoles) and sulfadiazine (5 g, 20.0 mmoles) were heated in a sand bath without a solvent at 140°C for (15 min). The solid product formed was washed with pet. Ether (40–60), collected by filtration, and then recrystallized from ethanol/acetic acid as colorless crystals; yield (75%); mp 190°C; IRν cm^{-1} 3200(NH); 1700(CO); 1650(CO); MS: m/z = 334; Found: C, 50.28; H, 4.21; N, 16.75; S, 9.58; calcd. for $C_{14}H_{14}N_4O_4S$: C, 50.29; H, 4.22; N, 16.76; S, 9.59 %.

5-Cyano-4-(4-methoxyphenyl)-2-methyl-N-{4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}-6-thioxo-1,6-dihydropyridine-3-carboxamide (2)

A mixture of acetoacetanilide (1) (3.34 g, 10.0 mmoles) and p-methoxy benzylidinecyanothioacetamide (2.18 g, 10.0 mmoles) in ethanol (50 mL) cotaining a catalytic amount of TEA was heated under reflux for 2 h. The solid product formed was collected by filtration and recrystallized from ethanol as yellow crystals; yield 60%; mp 220°C; IRν cm^{-1} 3300 (NH); 2250 (CN); 1650 (CO); MS: m/z = 532; Found: C, 56.36; H; 3.78; N, 15.77; S, 12.03; calcd. for $C_4H_{18}N_6O_4S_2$: C, 56.38; H, 3.79; N, 15.78; S, 12.04%.

2-Substituted-({3-cyano-4-(4-methoxyphenyl)-6-methyl-5-[4-(pyrimidin-2-ylamino) carbonyl]pyridine-2-yl-}thione (7a–e): General Procedure

To a solution of pyridinethione 2 (0.1 g, 5.0 mmoles) in ethanol (30 mL) and sodium acetate (5.0 mmoles), the appropriate halocompound (0.005 mmoles) was added. The reaction mixture was heated under reflux for 1 h. The solid product formed after cooling was collected by filtration, washed with water several times, and recrystallized from the proper solvent.

Ethyl({3-Cyano-4-(4-methoxyphenyl)-6-methyl-5-[4-(pyrimidin-2-ylamino) carbonyl]pyridine-2-yl})thioacetamide (7a)

Compound (7a) was obtained as colorless crystals from 1,4-dioxane; yield 42%; mp 190°C; IRν cm^{-1} 3300 (NH); 3150 (NH); 2250 (CN); 1740 (CO); 1650 (CO); ^{1}H NMR ($CDCl_3$) δ = 1.2 (t, 3H, CH_3); 3.6 (s, 3H, OCH_3); 4.0 (s, 2H, CH_2); 4.2 (q, 2H, CH_2); 6.8–8.4 (m, 12H, Ar-H and NH); 8.6 (s, 1H, NH); MS: m/z = 618 (372 base peak); Found: C, 56.29; H, 4.23; N, 13.57; S, 10.36; calcd. for $C_{29}H_{26}N_6O_6S_2$: C, 56.30; H, 4.24; N, 13.58; S, 10.37%.

6-(Benzoylthio)-5-cyano-4-(4-methoxyphenyl)-2-methyl-N-{4-[(pyrimidin-2- ylamino)sulfonyl]phenyl}nicotinamide (7b)

Compound (7b) was obtained as white crystals from ethanol; yield 30%; mp 230°C; IRν cm^{-1} 3300 (NH); 3100 (NH); 2240 (CN); 1690 (CO); 1660 (CO); MS: m/z = 636; Found: C, 60.90; H, 4.02; N, 12.90; S, 9.85; calcd. for $C_{33}H_{26}N_6O_5S_2$: C, 60.91; H, 4.03; N, 12.91; S, 9.86%.

6-({2-[(4-Chlorophenyl)-2-oxoethyl}thio-5-cyano-4-(4-methoxy-phenyl)-2-methyl-N-{4-[(pyrimidin-2-ylamino)-sulfonyl]phenyl}nicotinamide (7c)

Compound (7c) was obtained as a white powder from ethanol; yield 20%; mp 260°C; IRν cm^{-1} 3400 (NH); 3200 (NH); 2250 (CN); 1700 (CO); 1650 (CO); MS: m/z = 700; Found: C, 56.62; H, 3.74; N, 13.99; S, 9.17; calcd. for $C_{33}H_{26}ClN_7O_5S_2$: C, 56.61; H, 3.74; N, 14.00; S, 9.16%.

6-({2-[(4-Tolyl)amino]-2-oxoethyl}thio-5-cyano-4-(4-methoxy-phenyl)-2-methyl-N-{4-[(pyrimidin-2-ylamino)-sulfonyl]phenyl}nicotinamide (7d)

Compound (7d) was obtained as yellowish white crystals from 1,4-dioxane; yield 50%; mp 275°C; IRν cm^{-1} 3300 (NH); 3150 (NH); 2900–2970 (CH aliphatic); 2250 (CN); 1670 (CO); 1650 (CO);^{1}H NMR (DMSO-d_6) δ = 2.1 (s, 3H, CH_3); 2.6 (s, 3H, CH_3); 3.6 (s, 3H, OCH_3); 3.8 (s, 2H, CH_2); 7.0–8.5 (m, 17H, Ar-H and NH); 10.3 (s, 1H, NH); 10.8 (s, 1H, NH); MS: m/z = 679 (680 M^{+1}); Found: C, 60.05; H, 4.29; N, 14.40; S, 9.42; calcd. for $C_{34}H_{29}N_7O_5S_2$: C, 60.07; H, 4.30; N, 14.42; S, 9.43%.

5-Cyano-4-(4-methoxyphenyl)-2-methyl-3-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}pyridine-6-yl-thio-acetamide (7e)

Compound (7e) was obtained as yellow crystals from ethanol; yield 40%; mp 290°C; IRν cm^{-1} 3300 (NH); 3100 (NH); 2260 (CN); 1660 (CO); MS: m/z = 589; Found: C, 55.02; H, 3.94; N, 16.62; S, 10.87; calcd. for $C_{27}H_{23}N_7O_5S_2$: C, 55.00; H, 3.93; N, 16.63; S, 10.88%.

2-Substituted-3-amino-4-(4-methoxyphenyl)-6-methyl-5-[({4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}amino)carbonyl]thieno[2,3-*b*]pyridine (8a–e): General Procedure

To a sample of (7a–e) (1 g) in absolute ethanol (30 mL), a few drops of sodium ethoxide was added. The reaction mixture was heated under

reflux for 1 h. The solid product formed after cooling was collected by filtration and recrystallized from the proper solvent.

Ethyl-3-Amino-4-(4-methoxyphenyl)-6-methyl-5-[({4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}amino)carbonyl]-thieno[2,3-*b*]pyridine-2-carboxylate (8a)

Compound (8a) was obtained as yellow crystals from 1,4-dioxane; yield 32%; mp > 300°C; IRν cm^{-1} 3400 (NH_2); 3200 (NH); 1730 (CO); 1650 (CO); ^{1}H NMR (DMSO-d_6) δ = 1.2 (t, 3H, CH_3); 2.4 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 4.2 (q, 2H, CH_2); 6.4 (s, 2H, NH_2); 7.0–7.8 (m, 11H, Ar-H); 8.1 (s, 1H, NH); 10.4 (s, 1H, NH); MS: m/z = 618; Found: C, 56.29; H, 4.23; N, 13.58; S, 10.36; calcd. for $C_{29}H_{26}N_6O_6S_2$: C, 56.30; H, 4.24; N, 13.58; S, 10.37%.

3-Amino-2-benzoyl-4-(4-methoxyphenyl)-6-methyl-N-{4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}thieno[2,3-*b*]pyridine-5-carboxamide (8b)

Compound (8b) was obtained as colorless crystals from ethanol; yield 30%; mp. >300°C; IRν cm^{-1} 3450 (NH_2); 3200 (NH); 1710 (CO); 1650 (CO); MS: m/z = 650; Found: C, 60.90; H, 4.02; N, 12.90; S, 9.85; calcd. for $C_{33}H_{26}N_6O_5S_2$: C, 60.9; H, 4.03; N, 12.91; S, 9.86%.

3-Amino-2-(4-chlorobenzoyl)-4-(4-methoxyphenyl)-6-methyl-N-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}thieno[2,3-*b*]-pyridine-5-carboxamide (8c)

Compound (8c) was obtained as white crystals from ethanol; yield 35%; mp. 290°C; IRν cm^{-1} 3400 (NH_2); 3250 (NH); 3100 (NH); 1690 (CO); 1650 (CO); MS: m/z = 700; Found: C, 56.60; H, 3.73; N, 13.99; S, 9.15; calcd. for $C_{33}H_{26}ClN_7O_5S_2$: C, 56.61; H, 3.74; N, 14.00; S, 9.16%.

3-Amino-4-(4-methoxyphenyl)-6-methyl-2-methyl-4-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}thieno[2,3-*b*]-pyridine- 5-carboxamide (8d)

Compound (8d) was obtained as colorless crystals from ethanol; yield 25%; mp. >300°C; IRν cm^{-1} 3400 (NH_2); 3200 (NH); 1700 (CO); 1650 (CO); MS: m/z = 679; Found: C, 60.05; H, 4.29; N, 14.40; S, 9.15; calcd. for $C_{34}H_{29}N_7O_5S_2$: C, 60.07; H, 4.30; N, 14.42; S, 9.43%.

3-Amino-4-(4-methoxyphenyl)-6-methyl-5[({4-[(pyrimidin-2-ylamino)sulfonyl] phenyl}amino)carbonyl]thieno[2,3-*b*]-pyridine-2-amide (8e)

Compound (8e) was obtained as yellowish white crystals from ethanol; yield 35%; mp 320°C; IRν cm^{-1} 3450 (NH_2); 3200 (NH); 1670 (CO); 1650 (CO);^{1}H NMR (DMSO-d_6) δ = 1.5 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 5.6 (s, 2H, NH_2); 7.0–7.8 (m, 11H, Ar-H); 8.2 (s, 2H, NH_2); 10.8 (s, 1H, NH); MS: m/z = 589 (590;M^{+1}); Found: C, 55.02; H, 3.94; N, 16.64; S, 10.87; calcd. for $C_{27}H_{23}N_7O_5S_2$: C, 55.00; H, 3.93; N, 16.63; S, 10.88%.

3-Amino-4-(4-methoxyphenyl)-6-methyl-5[({4-[(pyrimidin-2-ylamino)sulfonyl] phenyl}amino)carbonyl]thieno[2,3-*b*]-pyridine-2-sodium carboxalate (9)

A suspension of amino ester (8a) (1 g) in ethanolic sodium hydroxide (30 mL, 10%) was refluxed for 3 h. The solid product formed after cooling was collected by filtration, washed with ethnol, left to dry, and recrystallized from ethanol as wellow crystals; yield 28%; mp 245–248°C; IRν cm^{-1} 3450 (NH_2); 3300 (NH); 3100 (NH); 1700 (CO); 1660 (CO); MS: m/z = 612; Found: C, 52.92; H, 3.45; N, 13.71; S, 10.46; calcd. for $C_{27}H_{21}N_6NaO_6S_2$: C, 52.94; H, 3.46; N, 13.72; S, 10.47%.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)sulfonyl]phenyl}-4- oxo-3,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-*d*][1,3]oxazine-8-carboxamide (10)

Compound (9) (0.5 g) was refluxed in acetic anhydride (30 mL) for 3 h. The reaction mixture was left to stand at r.t. for 5 h. The solid product formed was collected by filtration and recrystallized from ethanol/acetic acid as colorless crystals; yield (20%); mp 280–282°C; IRν cm^{-1} 3300 (NH); 3200 (NH); 1710 (CO); 1650 (CO); ^{1}H NMR ($CDCl_3$) δ = 1.2 (s, 3H, CH_3); 1.8 (s, 3H, CH_3); 3.6 (s, 3H, OCH_3); 7.0–8.2 (m, 12H, Ar-H); 8.4 (s, 1H, NH); 9.0 (s, 1H, NH); MS: m/z = 614; Found: C, 56.65; H, 3.60; N, 13.66; S, 10.42; calcd. for $C_{29}H_{22}N_6O_6S_2$: C, 56.67; H, 3.61; N, 13.67; S, 10.43%.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)sulfonyl]phenyl}-4- oxo-3,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-8-carboxamide (11)

Method A

A suspension of compound (10) (0.61 g, 1.0 mmoles) in acetic acid containing ammonium acetate (0.001 mmoles) was refluxed for 3 h. The solid product formed after cooling was collected by filtration.

Method B

Compound (8e) (1 g) was refluxed in acetic anhydride (20 mL) for 3 h. The reaction mixture was poured onto ice/water and left to stand for 12 h. The solid product formed was collected by filtration and recrystallized from ethanol as colorless crystals; mp. 180°C; IRν cm^{-1} 3400 (NH); 3200 (NH); 1710 (CO); 1650 (CO);^{1}H NMR (DMSO-d_6) $\delta = 1.9$ (s, 3H, CH_3); 2.4 (s, 3H, CH_3); .4 (s, 3H, OCH_3); 7.0–7.8 (m, 11H, Ar-H); 8.1 (s, 1H, NH); 8.6 (s, 1H, NH); 10.8 (s, 1H, NH); MS: m/z = 613; Found: C, 56.75; H, 3.77; N, 15.97; S, 10.44; calcd. for $C_{29}H_{23}N_7O_5S_2$: C, 56.76; H, 3.78; N, 15.98; S, 10.45%.

3-Amino-2-(hydrazinocarbonyl)-4-(4-methoxyphenyl)-6-methyl-N-{4-(pyrimidin-2-ylamino)sulfonyl]phenyl}thieno-[2,3-*b*]pyridine-5-carboxamide (12)

To a solution of aminoester (8a) (0.61 g, 1.0 mmoles) in ethanol (30 mL), hydrazine hydrate (0.02 mmoles) was added. The reaction mixture was refluxed for 3 h. The solid product formed was collected by filtration and recrystallized from ethanol as yellowish white crystals; yield 24%; mp 280°C; IRν cm^{-1} 3500 (NH_2); 3400 (NH); 3200 (NH); 1680 (CO);^{1}H NMR (DMSO-d_6) $\delta = 2.4$ (s, 3H, CH_3); 3.6 (s, 3H, OCH_3); 5.6 (s, 2H, NH_2); 6.4 (s, 1H, NH); 7.0-8.0 (m, 11H, Ar-H); 8.2 (s, 2H, NH_2); 10.5 (s, 1H, NH); MS: m/z = 604; Found: C, 53.62; H, 3.99; N, 18.52; S, 10.60; calcd. for $C_{27}H_{24}N_8O_5S_2$: C, 53.63; H, 4.00; N, 18.53; S, 10.61%.

9-(4-Methoxyphenyl)-7-methyl-N-{4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}-4-oxo- 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (13)

Method A

A suspension of amino ester 8a (0.61 g, 1.0 mmoles) in formamide (10 mL) was heated under reflux for 3 h, and the reaction mixture was poured onto ice/water. The solid product formed was collected by filtration, washed with water several times, and dried.

Method B

To a solution of (8e) (0.59 g, 1.0 mmoles) in acetic acid (30 mL), triethylorthoformate (3 mL) was added. The reaction mixture was refluxed for 3 h. The solid product formed was collected by filtration and recrystallized from 1,4-dioxane as colorless crystals; yield 55%; mp > 360°C; IRν cm^{-1} 3400 (NH); 3200 (NH); 1710 (CO); 1660 (CO);^{1}H NMR (DMSO-d_6) $d\delta = 2.4$ (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 7.0–8.0 (m, 11H, Ar-H); 8.1

(s, 1H, pyrimidine-H); 8.4 (s, 1H, NH); 10.7 (s, 1H, NH); MS: m/z = 599; Found: C, 56.07; H, 3.52; N, 16.34; S, 10.68; calcd. for $C_{28}H_{21}N_7O_5S_2$: C, 56.08; H, 3.53; N, 16.35; S, 10.69%.

Ethyl-3-(Acetylamino)-4-(4-methoxyphenyl)-6-methyl-5[{4-[(pyrimidin-2- ylamino)sulfonyl]phenyl}carbonyl]thieno-[2,3-*b*]pyridine-2-carboxalate(14)

A solution of aminoester (8a) (0.61 g, 1.0 mmoles) in acetic acid/acetic anhydride (30:3 mL), a mixture was heated under reflux for 4 h. The solid product formed after cooling was collected by filtration and recrystallized from DMF/water as colorless crystals; yield (45%); mp. 285°C; IRν cm^{-1} 3450 (NH); 3300 (NH); 3200 (NH); 1700 (CO); 1660 (CO);^{1}H NMR (DMSO-d_6) δ = 1.9 (s, 3H, CH_3); 2.2 (s, 3H, CH_3); 2.6 (t, 3H, CH_3); 3.1 (s, 3H, OCH_3); 3.8 (q, 2H, CH_2); 5.7 (s, 1H, NH); 7.0–8.0 (m, 12H, Ar-H); 10.8 (s, 1H, NH); MS: m/z = 660; Found: C, 56.34; H, 4.23; N, 12.70; S, 9.70; calcd. for $C_{31}H_{28}N_6O_7S_2$: C, 56.35; H, 4.24; N, 12.72; S, 9.71%.

3-(Acetylamino)-4-(4-methoxyphenyl)-6-methyl-N^5-{4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}-N^2-arylthieno[2,3-*b*]-pyridine-2,5-dicarboxamide (15a–c): General procedure

To a solution of compound (14) (0.66 g, 1.0 mmoles) in ethanol (30 mL), the appropriate aniline derivative (1.0 mmoles) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed was collected by filtration and recrystallized from the proper solvent.

3-(Acetylamino)-4-(4-methoxyphenyl)-6-methyl-N^5-{4-[(pyrimidin-2-ylamino) sulfonyl]phenyl}-N^2-phenylthieno-[2,3-*b*]pyridine-2,5-dicarboxamide (15a)

Compound 15a was obtained as pale yellow crystals from acetic acid; yield 42%; mp. 300°C; IRν cm^{-1} 3450 (NH); 3300 (NH); 1680 (CO); 1660 (CO); ^{1}H NMR (DMSO-d_6) δ = 1.6 (s, 3H, CH_3); 2.0 (s, 3H, CH_3); 3.2 (s, 3H, OCH_3); 6.4 (s, 1H, NH); 7.0–8.0 (m, 16H, Ar-H); 8.6 (s, 1H, NH); 10.8 (s, 1H, NH); MS: m/z = 707; Found: C, 59.37; H, 4.12; N, 13.86; S, 9.05; calcd. for $C_{35}H_{29}N_7O_6S_2$: C, 59.39; H, 4.13; N, 13.85; S, 9.06%.

3-(Acetylamino)-4-(4-methoxyphenyl)-6-methyl-N^5{4-[(pyrimidin-2-ylamino)- sulfonyl]phenyl}-N^2-(4-tolyl)thieno [2,3-*b*]pyridine-2,5-dicarboxamide (15b)

Compound 15b was obtained as white crystals from ethanol; yield 30%; mp. 320°C; IRν cm^{-1} 3300 (NH); 3100 (NH); 1700 (CO); 1650 (CO); MS:

m/z = 721(722 M^{+1}); Found: C, 59.92; H, 4.34; N, 13.59; S, 8.89; calcd. for $C_{36}H_{31}N_7O_6S_2$: C, 59.90; H, 4.33; N, 13.58; S, 8.88%.

3-(Acetylamino)-4-(4-methoxyphenyl)-6-methyl-N^5-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-N^2-(4-chlorlphenyl)-thieno[2,3-*b*]pyridine-2,5-dicarboxamide (15c)

Compound 15c was obtained as yellow crystals from 1,4-dioxane; yield 25%; mp > 360°C; IRν cm^{-1} 3400 (NH); 3200 (NH); 1690 (CO); 1650 (CO); MS: m/z = 724; Found: C, 56.63; H, 3.79; N, 13.20; S, 8.62; calcd. for $C_{35}H_{28}ClN_7O_6S_2$: C, 56.63; H, 3.80; N, 13.21; S, 8.64%.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)sulfonyl]phenyl}-4-oxo-3-substituted-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (16a-c): General Procedure

A suspension of compound 15a–c (1g) in 98% sulphuric acid (5 mL) was stirred for 1 h, and then left at r.t. for 5 days. The solid product formed after pouring the clear solution on ice water (100 mL) was collected by filtration, washed with water, dried, and recrystallized from the proper solvent.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)sulfonyl]phenyl}-4- oxo-3-phenyl-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (16a)

Compound 16a was obtained as colorless crystals from 1,4-dioxane; yield 30%; mp > 360°C; IRν cm^{-1} 3400 (NH); 3300 (NH); 1700 (CO); 1640 (CO); ^{1}H NMR (DMSO-d_6) δ = 2.4 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 6.8 (s, 1H, NH); 7.0–7.6 (m, 12H, Ar-H); 10.4 (s, 1H, NH); MS: m/z = 689; Found: C, 60.92; H, 3.94; N, 14.20; S, 9.28; calcd. for $C_{35}H_{27}N_7O_5S_2$: C, 60.94; H, 3.95; N, 14.21; S, 9.30%.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)sulfonyl]phenyl}-4-oxo-3-(4-tolyl)-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (16b)

Compound 16b was obtained as colorless crystals from ethanol/acetic acid; yield 20%; mp >360°C; IRν cm^{-1} 3400 (NH); 3100 (NH); 1710 (CO); 1660 (CO); MS: m/z = 703; Found: C, 61.42; H, 4.14; N, 13.92; S, 9.10; calcd. for $C_{36}H_{29}N_7O_5S_2$: C, 61.44; H, 4.15; N, 13.93; S, 9.11%.

9-(4-Methoxyphenyl)-2,7-dimethyl-N-{4-[(pyrimidin-2-lamino)-sulfonyl]phenyl}-4-oxo-3-(4-chlorophenyl)-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (16c)

Compound 16c was obtained as yellow crystals from methanol; yield 25%; mp > 360°C; IRν cm^{-1} 3300 (NH); 3200 (NH); 1700 (CO); 1650 (CO); MS: m/z = 724; Found: C, 58.05; H, 3.61; N, 13.53; S, 8.87; calcd. for $C_{35}H_{26}ClN_7O_5S_2$: C, 58.05; H, 3.62; N, 13.54; S, 8.86%.

9-(4-Methoxyphenyl)-7-methyl-N-{4-[(pyrimidin-2-ylamino)-sulfonyl]phenyl}-4-oxo-2-thio-3,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-8-carboxamide (17)

A suspension of 8e (0.58 g, 1.0 mmoles) and carbon disulfide (2 mL) in dioxane (20 mL) was heated under reflux for 8 h. The solid product formed after cooling was collected by filtration and recrystallized from ethanol as colorless crystals; yield 35%; mp 320°C; IRν cm^{-1} 3300 (NH); 3100 (NH); 1700 (CO); 1660 (CO); MS: m/z = 631 ($632M^{+1}$); Found: C, 53.23; H, 3.34; N, 15.51; S, 15.24; calcd. for $C_{28}H_{21}N_7O_5S_3$: C, 53.24; H, 3.35; N, 15.52; S, 15.23%.

9-(4-Methoxyphenyl)-7-methyl-N-{4-[(pyrimidin-2-ylamino)-sulfonyl]phenyl}-4-oxo- 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]triazine-8-carboxamide (18)

To a cold solution of 8e (0.58 g, 10.0 mmoles) in acetic acid (30 mL), a cold solution of sodium nitrite (1 g in 2 mL of H_2O) was added dropwise with stirring. The stirring was continued for 1 h and left to stand at r.t. for 1 h. The solid product formed was collected by filtration and recrystallized from 1,4-dioxane; yield 30%; mp. 280°C; IRν cm^{-1} 3400 (NH); 3200 (NH); 1690 (CO); 1650 (CO); ^{1}H NMR (DMSO-d_6) $\delta = 2.4$ (s, 3H, CH_3); 3.6 (s, 3H, OCH_3); 7.0–7.8 (m, 11H, Ar-H); 8.4 (s, 1H, NH); 10.8 (s, 1H, NH); MS: m/z = 600; Found: C, 53.97; H, 3.35; N, 18.68; S, 10.67; calcd. for $C_{27}H_{20}N_8O_5S_2$: C, 53.99; H, 3.36; N, 18.66; S, 10.68%.

4-Chloro-9-(4-methoxyphenyl)-7-methyl-N-{4-[(pyrimidin-2-ylamino)sulfonyl] phenyl}-4-3,4-dihydropyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine-8-carboxamide (19)

A suspension of compound 13 (0.59 g, 1.0 mmoles) in $POCl_3$ (10 mL) was refluxed for 2 h and then left to stand at r.t. The reaction mixture was poured onto ice/water, and the solid product formed was collected by

filtration, washed with water several times, dried, and recrystallized from ethanol/acetic acid as red crystals; yield 35%; mp >360°C; IRν cm^{-1} 3300 (NH); 3100 (NH); 1700 (CO); 1650 (CO); MS: m/z = 617; Found: C, 54.40; H, 3.25; N, 15.85; S, 10.37; calcd. for $C_{28}H_{20}ClN_7O_4S_2$: C, 54.41; H, 3.26; N, 15.86; S, 10.38%.

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