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Pyridine-2(1*H*)-thione in heterocyclic synthesis: synthesis and antimicrobial activity of some new thio-substituted ethyl nicotinate, thieno[2,3-*b*]pyridine and pyridothienopyrimidine derivatives

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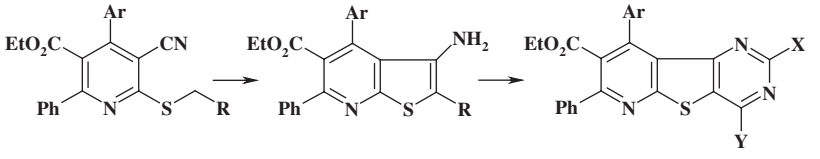
3-(4-Bromophenyl)-2-cyanoprop-2-enethioamide (**1**) reacted with ethyl 3-oxo-3-phenylpropanoate (**2**) to give ethyl 4-(4-bromophenyl)-5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (**3**). Compound **3** was taken as a starting material for the synthesis of thio-substituted ethyl nicotinate derivatives **5a**–**d**, which underwent cyclization to the corresponding thieno[2,3-*b*]pyridines **6a**–**d**. Also **3** reacted with hydrazine hydrate to give the pyrazolo[3,4-*b*]pyridine derivative **7**, which upon diazotization gave the diazonium derivative **8**. Compound **6a** condensed with dimethylformamide–dimethylacetal to afford thieno[2,3-*b*]pyridine derivative **9**, which reacted with different amines **10a**–**e** to afford the pyridothienopyrimidine derivatives **12a**–**e** through the Dimroth rearrangement. Moreover, compound **6a** reacted with different reagents to give pyridothienopyrimidine derivatives **14a** and **b**, **17** and pyrazolothienopyridine derivative **18**. In addition, acetylating compound **6c** with chloroacetylchloride afforded the 3-[(2)-chloroacetylamino]thieno[2,3-*b*]pyridine derivative **20**, which upon cyclization yielded the corresponding 2-chloromethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivative **21**. Some of the newly synthesized compounds were screened *in vitro* for their antimicrobial activities.



Keywords: pyridine-2(1*H*)-thione; thio-substituted ethyl nicotinate thieno-[2,3-*b*]pyridines; pyridothienopyrimidines; antimicrobial activity

1. Introduction

In the last decade, our research group has paid attention to the synthesis and biological activities of heterocyclic derivatives widely used in medicinal and pharmaceutical chemistry and several

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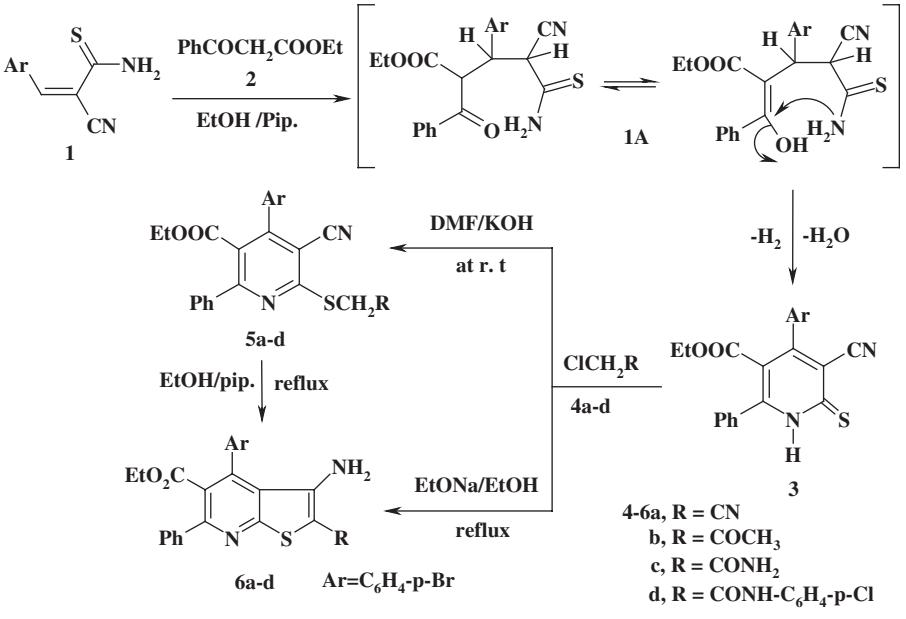
publications have appeared concerning the synthesis of new pyridine and annulated pyridine derivatives (*1–11*) of biological interest.

Recently, ethyl nicotinate derivatives were reported to exhibit antimicrobial (*3*) and vasodilatory (*12*) activities and were used as anticancer (*13*) agents. Moreover, thieno[2,3-*b*]pyridines derivatives are of special importance due to their reported chemical and biological activities. In particular, in a recent review, it was reported (*14*) that they also act as anti-Alzheimer and anti-COX-2 (*1, 2, 7*), inhibitors of Protein Kinase C theta, as anti-inflammatories (*15*), as eukaryotic elongation factor-2 kinase inhibitors (*16*), as anti-diabetics (*17*), as potent antiviral (*18, 19*), antimicrobial (*3, 20*) and anticancer (*5, 21*) agents. In addition, pyridothienopyrimidines have found applications as anti-Alzheimer and anti-COX-2 (*1, 7*), antiviral (*22*), anti-tumor (*22*), anti-dermatophytic (*23*), anti-allergic (*24*), anticancer (*25*), anti-protozoals (*26*) and antibacterial (*3*) agents. As a result of these findings, and as a continuation of our recent synthetic efforts and studies of the biological activities of pyridine and annulated pyridine derivatives of expected biological activity, we reported herein the synthesis and antibacterial activities of some new ethyl nicotinate, thieno[2,3-*b*]pyridine and pyridothienopyrimidine derivatives.

2. Results and discussion

It has been found that 3-(4-bromophenyl)-2-cyanoprop-2-enethioamide (**1**) (available from Akos GmbH and can be prepared from the reaction of 2-cyanoethanethioamide and 4-bromobenzaldehyde under stirring in ethanolic/piperidine solution at room temperature using the method reported in the literature (*27*)) reacted with ethyl 3-oxo-3-phenylpropanoate (**2**) in ethanol containing catalytic amount of piperidine under reflux to give the corresponding ethyl 4-(4-bromophenyl)-5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (**3**), whose structure was confirmed based on elemental analysis and spectral data. Its IR spectrum indicated the presence of absorption bands for NH, CN and CO functional groups at 3145, 2227 and 1721 cm^{-1}, respectively, while its ^{1}H NMR spectrum revealed signals of ethyl protons at $\delta = 0.64$–0.67 ppm (t, $J = 7.0$ Hz, 3H, CH_3) and 3.62–3.75 (q, $J = 7.0$ Hz, 2H, CH_2), aromatic protons at $\delta = 7.38$–7.78 ppm (m, 9H) and an NH proton at $\delta = 14.65$ ppm. The formation of compound **3** in this reaction was assumed to proceed via Michael addition of the active methylene compound **2** to the double bond in compound **1** to afford the intermediate adduct **1A**, which underwent cyclization with the loss of one molecule of water and hydrogen to yield the isolated reaction product **3** (see Scheme 1 and Section 4).

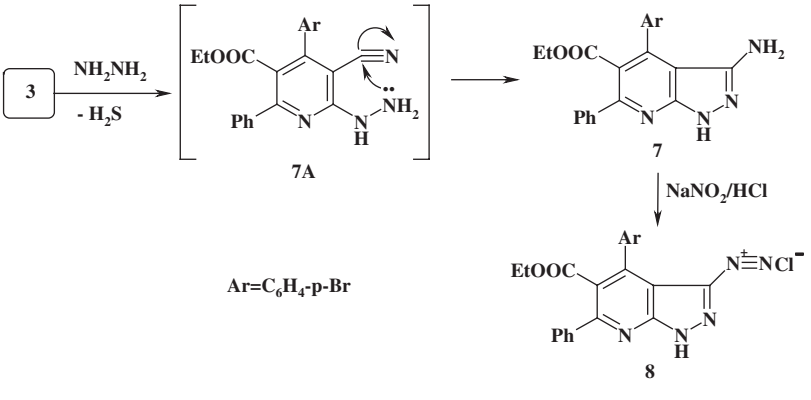
Compound **3** reacted with chloroacetonitrile (**4a**) in KOH/dimethylformamide (DMF) solution under stirring at room temperature to afford the corresponding ethyl nicotinate derivative **5a** via dehydrochlorination. The structure of **5a** was confirmed by elemental analysis and spectral data. The IR spectrum of **5a** showed the presence of absorption bands due to two C≡N at 2246 and 2222 cm^{-1} and a C=O at 1725 cm^{-1}, while its ^{1}H NMR spectrum revealed a signal for SCH_2 at $\delta = 4.26$ ppm. In a similar manner, compound **3** reacted with chloroacetone (**4b**), chloroacetamide (**4c**) and *N*-(4-chlorophenyl)chloroacetamide (**4d**) to afford the corresponding ethyl nicotinate derivatives **5b**–**d**. The ^{1}H NMR spectrum of compound **5d** exhibited two singlets at $\delta = 4.32$ and 10.54 ppm, respectively, assignable to SCH_2 and NH. The structure of compounds **5a**–**d** was further elucidated via its cyclization to the corresponding thieno[2,3-*b*]pyridine derivatives **6a**–**d** upon boiling in ethanol-containing piperidine. The IR spectra of compounds **6a**–**d** showed the presence of the absorption bands of the newly formed NH_2 group. The ^{1}H NMR spectrum of compound **6a** also exhibited a singlet at $\delta = 5.53$ ppm assignable to NH_2 (see Scheme 1 and Section 4).



Scheme 1. Synthesis of ethyl nicotinate and thienopyridine derivatives.

Unequivocal support for the structures of **6a**–**d** was achieved via their synthesis by an alternative route via the reaction of **3** and **4a**–**d** in ethanolic sodium ethoxide solution under reflux to give the same reaction products **6a**–**d** as described above (see Scheme 1 and Section 4).

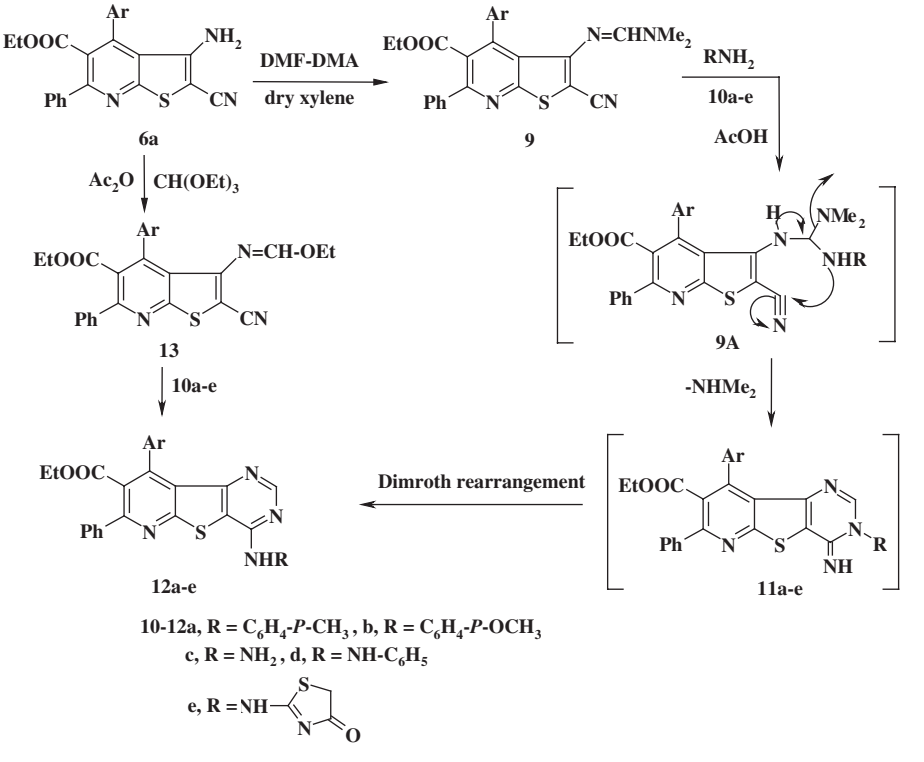
Treatment of **3** with hydrazine hydrate under reflux afforded a sulfur-free reaction product based on elemental analysis. The IR spectrum of the reaction product indicated the absence of the absorption bands due to a CN functional group but the absorption bands of the newly formed NH_2 were detected at 3422 and 3335 cm^{-1}. In addition, absorption bands for NH and COOEt functional groups were observed at 3210 and 1720 cm^{-1}, respectively. Its ^1H NMR spectrum showed the signals for CH_2CH_3 as a triplet and quartet with $J = 7.0$ Hz, NH_2 at $\delta = 4.45$ ppm and NH at $\delta = 12.63$ ppm in addition to the aromatic protons. Accordingly, this reaction product was formulated as ethyl 3-amino-4-(4-bromophenyl)-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**7**) (Scheme 2).



Scheme 2. Synthesis of pyrazolopyridine derivatives.

The formation of compound **7** in the above-mentioned reaction was assumed to proceed via nucleophilic attack of the hydrazine molecule on the 6-thioxopyridine derivative **3** with elimination of hydrogen sulfide (detected with a lead acetate paper) to give the intermediate hydrazino derivative **7A**, which underwent cyclization into the final reaction product **7**. Compound 7 upon diazotization afforded the stable isolated (*28*), 4-(4-bromophenyl)-5-(ethoxycarbonyl)-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-diazonium chloride (**8**) (see Scheme 2 and Section 4).

Condensation of **6a** with DMF–dimethylacetal (DMA) in dry xylene under reflux, yielded the corresponding 3-{[(*N*,*N*-dimethylamino)methylene]amino}-3-cyanothieno[2,3-*b*]pyridine derivative **9**. The IR spectrum of **9** showed the absence of the absorption bands due to the NH_2 group while its ^{1}H NMR revealed the presence of two singlets at $\delta = 2.79$ and 2.87 ppm for $N(CH_3)_2$ as a result of the restricted rotation around the N=C bond, a signal at 7.62 ppm for the N=CH proton and the absence of any signals corresponding to NH_2 protons (see Scheme 3 and Section 4).



Scheme 3. Synthesis of pyridothienopyrimidine derivatives.

The reactivity of 3-{[(*N*,*N*-dimethylamino)methylene]amino}-3-cyanothieno[2,3-*b*]pyridine derivative **9** toward aromatic amines was investigated. Thus, **9** reacted with 4-methyltoluidine (**10a**) in acetic acid to afford the corresponding 4-(4-methylphenyl)pyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine derivative **12a** via the loss of one molecule of dimethylamine (see Scheme 3 and Section 4).

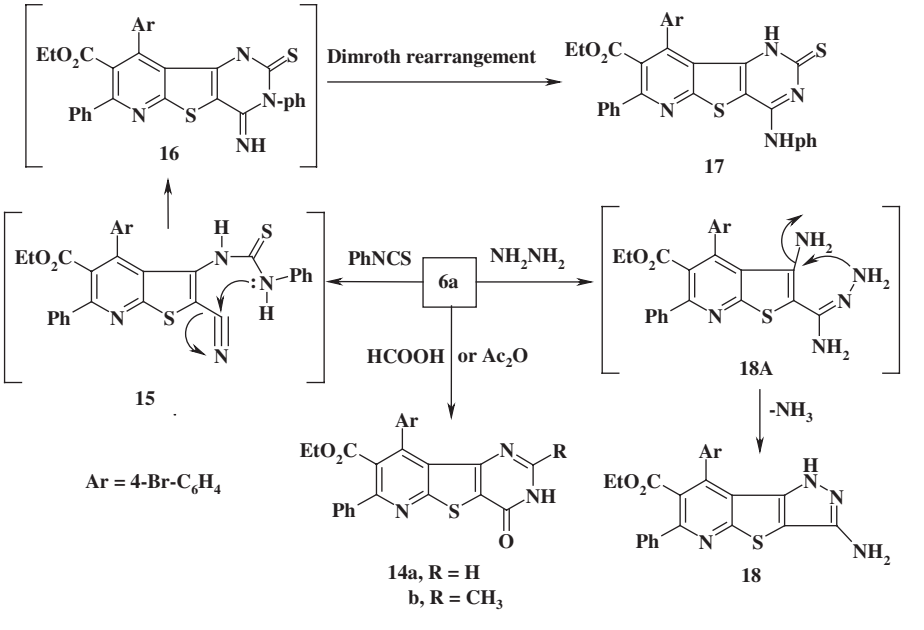
The IR spectrum of **12a** indicated the absence of a CN group and the presence of NH at 3180 cm^{-1}, while its ^{1}H NMR spectrum revealed the signals for additional CH_3 protons at

$\delta = 2.36$ ppm and NH protons at $\delta = 9.79$ ppm and an absence of the signal for $N(CH_3)_2$ protons. The formation of **12a** in this reaction is assumed to proceed through the addition of **10a** to **9** to give the addition product **9A** followed by cyclization with the loss of dimethylamine to give the intermediate imino derivative **11a** which underwent *Dimroth* rearrangement (*29, 30*), under the reaction conditions to yield **12a** (see Scheme 3 and Section 4).

Compound **9** reacted in a similar manner with 4-methoxyaniline (**10b**), hydrazine hydrate (**10c**), phenyl hydrazine (**10d**) and 2-hydrazino-1,3-thiazol-4(5*H*)-one (**10e**) under the same reaction conditions to yield the corresponding pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **12b–e**. The structure of **12b–e** was elucidated based on elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{13}C NMR spectra of compounds **12c–e** were found to be in good agreement with the assigned structures (see Scheme 3 and Section 4).

Convincing evidence for structures **12a–e** came from their independent syntheses through an alternative route, via reaction of **6a** with triethylorthoformate in acetic anhydride and subsequent condensation of the so-formed 2-cyano-3-[(ethoxymethylene)amino]thieno[2,3-*b*]pyridine derivative **13** with **10a–e** to afford the products which were identical in all respect (m.p., mixed m.p. and spectral data) with the previously described **12a–e** (see Scheme 3 and Section 4).

The work was extended to study the reactivity of 2-cyano-3-aminothieno[2,3-*b*]pyridine derivative **6a** toward several other nucleophiles. Thus, treatment of compound **6a** with formic acid or acetic anhydride under reflux afforded the pyridothienopyrimidine derivatives **14a** and **b**, respectively. The IR spectra of **14a** and **b** showed the absence of the absorption bands corresponding to NH_2 and CN groups and the presence of the amidic carbonyl group at 1674 and 1657 cm^{-1}, respectivly. The ^{1}H NMR spectrum of **14a** revealed signals at $\delta = 8.13$ (s, 1H, C_2H) and 12.87 (s, 1H, NH) (Scheme 4).

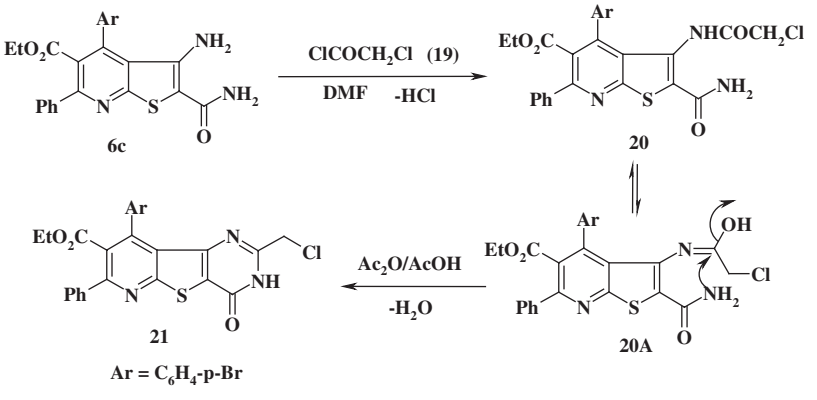


Scheme 4. Synthesis of pyridothienopyrimidine derivatives.

Moreover, when **6a** was allowed to react with phenylisothiocyanate in pyridine under reflux, the corresponding pyridothienopyridimidine derivative **17** was obtained. The formation of **17** in

this reaction is assumed to proceed through addition of NH_2 in **6a** to the phenylisothiocyanate to give the non-isolable thiourea derivative **15** which cyclized to the imino derivative **16** that subsequently underwent the *Dimroth* rearrangement (*31*), under the reaction conditions to yield **17**. In addition, compound **6a** reacted with hydrazine hydrate to give the pyrazolothienopyridine derivative **18**, which formed via the addition of one molecule of hydrazine to the cyano group in compound **6a** to give the non-isolated addition product **18A**, which cyclized to form **18** with the loss of ammonia. The IR spectrum of **18** showed the absence of an absorption band corresponding to a CN group. The ^{1}H NMR spectrum of **18** revealed signals at $\delta = 5.25$ (s, 2H, NH_2) and 7.99 (s, 1H, NH). In addition, its ^{13}C NMR was in good agreement with the assigned structure (see Scheme 4 and Section 4).

Work was also extended to study the reactivity of the aminocarboxamide system in compound **6c**. Thus, acetylation of compound **6c** with chloro acetylchloride **19** in DMF solution with stirring at room temperature afforded the corresponding 3-[(2-chloroacetyl)amino]thieno[2,3-*b*]pyridine derivative **20**. The IR spectrum of compound **20** showed the presence of NH_2 and NH groups at 3467, 3336 and 3176 cm^{-1} and two carbonyl functional groups at 1727 and 1673 cm^{-1}. The $CONH_2$ protons were also detected in its ^{1}H NMR spectrum at $\delta = 7.24$ ppm. Cyclization of compound **20** via heating in a mixture of acetic anhydride and acetic acid yielded the corresponding 2-chloromethyl-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivative **21** via the loss of water molecule from the tautomer **20A**. The IR and ^{1}H NMR specta of **21** revealed the absence of $CONH_2$ protons (see Scheme 5 and Section 4).



Scheme 5. Reaction of **6c** with chloro acetylchloride.

3. Biological activity

Ten of the synthesized compounds were screened *in vitro* for their biological activities against two strains of bacteria and two fungi, "*Escherichia coli*, *Staphylococcus aureus*, *Aspergillus flavus and Candida albicans*". A filter paper-sterilized disc saturated with a measured quantity of the sample is placed on a plate containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Doxs medium), which has been heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (*32*). The diameter of inhibition zones (mm/mg sample) are reported in Table 1. The results indicated that most of the tested compounds exhibit mild to strong activities against bacteria but are inactive against fungi except compound **12c**, which was found to be highly active against *A. flavus*.

Table 1. The antimicrobial activity of some newly synthesized compounds (diameter of inhibition zone in mm/mg sample).

Inhibition zone diameter (mm/mg sample)				
Compound no.	*E. coli* (Gram −ve)	*S. aureus* (Gram +ve)	*A. flavus*	*C. albicans*
Control: DMSO	0.0	0.0	0.0	0.0
5a	13	12	0.0	0.0
5c	14	15	0.0	0.0
6b	12	12	0.0	0.0
9	11	11	0.0	0.0
12a	11	11	0.0	0.0
12c	14	14	16	0.0
14a	14	14	0.0	0.0
20	13	13	0.0	0.0
21	12	12	0.0	0.0
Ampicillin	22	23	–	–
Flucoral	–	–	15	16

Notes: Nil, 0; less active, 2–6 mm; moderately active, 7–12 mm; highly active, 13–20 mm.

4. Experimental

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on a BRUKER Vector 22 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed in δ ppm units and the coupling constant J in Hz. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses and the antimicrobial screening were carried out at the Microanalytical Center of Cairo University.

4.1. *Ethyl 4-(4-bromophenyl)-5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (3)*

A mixture of 3-(4-bromophenyl)-2-cyanoprop-2-enethioamide (**1**) (10 mmol) and ethyl 3-oxo-3-phenylpropanoate (**2**) in ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml) was heated under reflux for 6 h, then cooled and acidified with acetic acid. The solid product that formed was collected by filtration, dried and crystallized from ethanol to give **3** as yellow crystals, (69%), m.p. 266-268 °C, IR υ (cm^{-1}): 3145 (NH), 2227 (CN), 1721 (CO-ester). ^{1}H NMR (DMSO-d_6): δ 0.64–0.67 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$); 3.62–3.75 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$); 7.38–7.78 (m, 9H, Ar–H) and 14.65 (s, 1H, NH). Anal. for $C_{21}H_{15}BrN_2O_2S$ (439.3): Calcd.: C, 57.41; H, 3.44; N, 6.38; S, 7.30; Br, 18.19%. Found: C, 57.20; H, 3.80; N, 6.61; S, 7.06; Br, 18.40%.

4.2. *Reaction of 3 with α-halocarbonyl compounds 4a–d: general procedure*

A mixture of compound **3** (10 mmol) and each of the compounds **4a**–**d** (10 mmol) in DMF (30 ml) containing KOH (12 mmol) were stirred at room temperature for 2 h, then poured onto ice-cold water and acidified with dil. HCl. The solid products were filtered off, washed with water and crystallized from ethanol to give compounds **5a**–**d**, respectively.

4.3. *Ethyl 4-(4-bromophenyl)-5-cyano-6-[(cyanomethyl)thio]-2-phenylnicotinate (5a)*

Yellow crystals (68%, ethanol), m.p. 186°C, IR υ (cm^{-1}): 3061 (aromatic CH), 2246, 2222 (2CN), 1725 (CO-ester), 1606 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.74–0.88 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.72–3.89 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.26 (s, 2H, SCH_2) and 7.40–7.84 (m, 9H, Ar–H). Anal. for $C_{23}H_{16}N_3O_2SBr$ (478.3): Calcd.: C, 57.75; H, 3.37; N, 8.78; S, 6.70; Br, 16.70. Found: C, 57.54; H, 3.14; N, 8.60; S, 6.92; Br, 16.51%.

4.4. *Ethyl 4-(4-bromophenyl)-5-cyano-6-[(2-oxopropyl)thio]-2-phenylnicotinate (5b)*

Yellow crystals (64%, ethanol), m.p. 162°C, IR υ (cm^{-1}): 2220 (CN), 1721 (CO-ester), 1628 (C=N). Anal. for $C_{24}H_{19}N_2O_3SBr$ (495.3): Calcd.: C, 58.19; H, 3.87; N, 5.65; S, 6.47; Br, 16.13. Found: C, 58.40; H, 3.64; N, 5.50; S, 6.70; Br; 16.00%.

4.5. *Ethyl 6-[(2-amino-2-oxoethyl)thio]-4-(4-bromophenyl)-5-cyano-2-phenylnicotinate (5c)*

Yellow crystals (70%, ethanol), m.p. 216°C, IR υ (cm^{-1}): 3445, 3145 (NH_2), 2220 (CN), 1721 (CO-ester); 1689 (amidic CO), 1601 (C=N). Anal. for $C_{23}H_{18}N_3O_3SBr$ (496.3): Calcd.: C, 55.65; H, 3.66; N, 8.47; S, 6.46; Br; 16.10. Found: C, 55.87; H, 3.70; N, 8.30; S, 6.20; Br; 16.33%.

4.6. *Ethyl 4-(4-bromophenyl)-6-({2-[(4-chlorophenyl)amino]-2-oxoethyl}thio)-5-cyano-2-phenylnicotinate (5d)*

Yellowish white crystals from ethanol (64%), m.p. 228–230°C, IR υ (cm^{-1}): 3258 (NH), 2219 (CN), 1721 (CO-ester), 1659 (amidic CO). ^{1}H NMR (DMSO-d_6): δ 0.75–0.82 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.88–3.92 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.32 (s, 2H, SCH_2), 7.28–7.84 (m, 13H, Ar–H) and 10.54 (s, 1H, NH). Anal. for $C_{29}H_{21}N_3O_3SBrCl$ (606.9): Calcd.: C, 57.39; H, 3.49; N, 6.92; S, 5.28; Br, 13.17; Cl, 5.84. Found: C, 57.60; H, 3.73; N, 6.710; S, 5.62; Br, 13.37; Cl, 5.60%.

4.7. *Synthesis of compounds 6a–d*

4.7.1. *Route A: cyclization of compounds **5a–d***

A solution of compounds **5a**–**d** (10 mmol) in ethanol (30 ml) containing catalytic amount of piperidine (0.5 ml) was heated under reflux for 3 h. The solid products obtained after cooling were filtered off and crystallized from ethanol to afford compounds **6a**–**d**.

4.7.2. *Route B: reaction of **3** with **4a–d***

A mixture compound of **3** (10 mmol) and compounds **4a**–**d** (10 mmol) in ethanolic sodium ethoxide (prepared from 0.02 mol of sodium metal and 40 ml ethanol) was heated under reflux for 4 h and then cooled. The reaction mixtures were then poured onto ice-cold water and neutralized by dilute HCl. The solid products obtained were filtered off and crystallized from ethanol to give compounds **6a**–**d**.

4.8. *Ethyl 3-amino-4-(4-bromophenyl)-2-cyano-6-phenylthieno[2,3-b]pyridine-5-carboxylate (6a)*

Yellow crystals (68%, DMF/ethanol), m.p. 190°C, IR υ (cm^{-1}): 3471, 3322 (NH_2), 2207 (CN), 1720 (CO-ester), 1631 (C=N). ^1H NMR (DMSO-d_6): δ 0.75–0.82 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.80–3.88 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 5.53 (s, 2H, NH_2) and 7.48–7.86 (m, 9H, Ar–H). Anal. for $C_{23}H_{16}N_3O_2SBr$ (478.3): Calcd.: C, 57.75; H, 3.37; N, 8.78; S, 6.70; Br, 16.70. Found: C, 57.96; H, 3.64; N, 8.66; S, 6.92; Br, 16.95%.

4.9. *Ethyl 2-acetyl-3-amino-4-(4-bromophenyl)-6-phenylthieno[2,3-b]pyridine-5-carboxylate (6b)*

Yellow crystals (63%, ethanol), m.p. 214–216°C, IR υ (cm^{-1}): 3488, 3319 (NH_2), 1718 CO-ester), 1628 ($COCH_3$ with H-bond). Anal. for $C_{24}H_{19}N_2O_3SBr$ (495.3): Calcd.: C, 58.19; H, 3.87; N, 5.65; S, 6.47; Br, 16.13. Found: C, 58.32; H, 3.64; N, 5.45; S, 6.70; Br, 16.00%.

4.10. *Ethyl 3-amino-4-(4-bromophenyl)-2-carbamoyl-6-phenylthieno[2,3-b]pyridine-5-carboxylate (6c)*

Yellow crystals (68%, ethanol), m.p. 146°C, IR υ (cm^{-1}): 3478, 3319, 3172 (two NH_2), 1723 (CO), 1668 (amidic CO). ^1H NMR (DMSO-d_6): δ 0.76–0.83 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.79–3.90 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 5.76 (s, 2H, NH_2), 7.38 (s, 2H, NH_2) and 7.44–7.82 (m, 9H, Ar–H). Anal. for $C_{23}H_{18}N_3O_3SBr$ (496.3): Calcd.: C, 55.65; H, 3.66; N, 8.47; S, 6.46; Br, 16.10. Found: C, 55.31; H, 3.40; N, 8.25; S, 6.70; Br, 16.30%.

4.11. *Ethyl 3-amino-4-(4-bromophenyl)-2-[(4-chlorophenyl)carbamoyl]-6-phenylthieno-[2,3-b]pyridine-5-carboxylate (6d)*

Yellow crystals from ethanol (64%), m.p. 222–224°C, IR υ (cm^{-1}): 3487, 3351, 3254 (NH_2 and NH), 1713 (CO-ester), 1632 (C9O amide with H-bond). Anal. for $C_{29}H_{21}N_3O_3SBrCl$ (606.5): Calcd.: C, 57.39; H, 3.49; N, 6.92; S, 5.28; Br; 13.17; Cl, 5.84. Found: C, 57.76; H, 3.72; N, 6.70; S, 5.50; Br, 13.32; Cl, 5.60%.

4.12. *Ethyl 3-amino-4-(4-bromophenyl)-6-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (7)*

A mixture of compounds **3** (10 mmol) and hydrazine hydrate (20 ml) was heated under reflux for 24 h. The reaction mixture was cooled and evaporated under vaccum. The solid product obtained was filtered off and crystallized from ethanol to give compound **7** as yellow crystals (58%), m.p. 220°C, IR υ (cm^{-1}): 3422, 3335, 3210 (NH_2 and NH), 1720 (CO). ^1H NMR (DMSO-d_6): δ 0.70–0.77 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.75–3.82 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.45 (s, 2H, NH_2), 7.40–7.70 (m, 9H, Ar–H) and 12.63 (s, 1H, NH). Anal. for $C_{21}H_{17}N_4O_2Br$ (437.2): Calcd.: C, 57.68; H, 3.92; N, 12.81; Br, 18.27. Found: C, 57.47; H, 3.70; N, 12.60; Br, 18.51%.

4.13. *4-(4-Bromophenyl)-5-(ethoxycarbonyl)-6-phenyl-1H-pyrazolo[3,4-b]pyridine-3-diazonium chloride (8)*

A solution of compound **7** (10 mmol) in acetic acid (20 ml) containing 1 ml of concentrated HCl was stirred in an ice bath and then a cold saturated solution of 15 mmol of sodiun nitrite in water

was added. The reaction mixture was stirred for 1 h and the solid product thus formed was filtered off, washed with water and crystallized from ethanol to give **8** as yellow crystals (55%), m.p. 146°C (decompose), IR υ (cm^{-1}): 3364 (NH), 2127 (N:N) and 1720 (CO).

4.14. *Reaction of 6a with DMF-DMA*

A mixture of compounds **6a** (10 mmol) and DMF–DMA (13 mmol) in dry xylene (30 ml) was heated under reflux for 6 h. The reaction mixture was cooled and triturated with petroleum ether (40–60). The solid product obtained was filtered off and crystallized from ethanol to give compound **9**.

4.15. *Ethyl 4-(4-bromophenyl)-2-cyano-3-{[-(dimethylamino)methylene]amino}-6-phenylthieno[2,3-b]pyridine-5-carboxylate (9)*

Orange yellow crystals (62% dioxane), m.p. 186°C, IR υ (cm^{-1}): 3056 (aromatic CH), 2203 (CN), 1726 (CO), 1625 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.70–0.77 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 2.79, 2.87 (2s, 6H, $N(CH_3)_2$), 3.81–3.84 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.08–7.53 (m, 9H, Ar–H) and 7.62 (s, 1H, N=CH). Anal. for $C_{26}H_{21}N_4O_2SBr$ (533.4): Calcd.: C, 58.54; H, 3.97; N, 10.50; S, 6.01; Br, 14.94. Found: C, 58.76; H, 3.75; N, 10.30; S, 5.80; Br, 14.70%.

4.16. *Reaction of 9 with aromatic amines 10a–e*

A solution of **9** (10 mmol) in acetic acid (40 ml) was treated with **10a**–**e** (12 mmol). The reaction mixture was heated under reflux for 3 h and then cooled. The solid product obtained was filtered off and crystallized from the proper solvent to give compounds **12a**–**e**, respectively.

4.17. *Ethyl 9-(4-bromophenyl)-4-[(4-methylphenyl)amino]-7-phenylpyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (12a)*

Yellow crystals from ethanol, m.p. 248–250°C, IR υ (cm^{-1}): 3180 (NH), 1719 (CO-ester), 1605 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.80–0.87 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 2.36 (s, 3H, CH_3), 3.89–3.92 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.26 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.44 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.58–7.74 (m, 9H, Ar–H), 8.45 (s, 1H, $C_{(2)}$–H) and 9.79 (s, 1H, NH). Anal. for $C_{31}H_{23}N_4O_2SBr$ (5955): Calcd.: C, 62.52; H, 3.89; N, 9.41; S, 5.38; Br, 13.42. Found: C, 62.33; H, 3.70; N, 9.20; S, 5.65; Br, 13.61%.

4.18. *Ethyl 9-(4-bromophenyl)-4-[(4-methoxyphenyl)amino]-7-phenyl-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (12b)*

Yellow crystals from ethanol, m.p. 280–282°C, IR υ (cm^{-1}); 3195 (NH), 1727 (CO-ester), 1605 (C=N). Anal. for $C_{31}H_{23}N_4O_3S$ Br (611.5): Calcd.: C, 60.89; H, 3.79; N, 9.16; S, 5.24; Br, 13.07. Found: C, 60.63; H, 3.95; N, 9.37; S, 5.50; Br, 13.29%.

4.19. *Ethyl 9-(4-bromophenyl)-4-hydrazino-7-phenylpyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-8-carboxylate (12c)*

Yellow crystals from ethanol, m.p. 288–290°C, IR υ (cm^{-1}); 3352, 3294, 3223 (NH_2 and NH), 1720 (CO-ester), 1605 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.74–0.77 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$),

3.81–3.85 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.48 (s, 2H, NH_2), 7.32 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.50–7.53 (m, 5H, Ar–H); 7.62 (d, $J = 8.2$ Hz, 2H, Ar–H), 8.13 (s, 1H, $C_{(2)}$–H) and 9.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.30, 61.30, 102.99, 110.67, 121.93, 128.60, 130.49, 130.78, 131.39, 132.31, 133.00, 134.35, 135.36, 135.90, 138.90, 156.11, 159.38, 167.27; 185.16. Anal. for $C_{24}H_{18}N_5O_2SBr$ (520.4): Calcd.: C, 55.39; H, 3.49; N, 13.46; S, 6.16; Br, 15.35. Found: C, 55.63; H, 3.30; N, 13.72; S, 6.40; Br, 15.55%.

4.20. *Ethyl 9-(4-bromophenyl)-7-phenyl-4-(2-phenylhydrazino)pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-8-carboxylate (12d)*

Yellow crystals from acetic acid, m.p. 264°C, IR υ (cm^{-1}); 3275, 3176 (2NH), 1726 (CO-ester); 1605 (C=N), ^{1}H NMR (DMSO-d_6): δ 0.72–0.79 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.78–3.88 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 6.80–7.25 (m, 5H, Ar–H), 7.35 (d, $J = 8.2$ Hz, Ar–H), 7.46–7.52 (m, 5H, Ar–H), 7.58 (d, $J = 8.2$ Hz, Ar–H), 8.32 (s, 1H, $C_{(2)}$–H), 8.50 (s, 1H, NH) and 9.94 (s, 2H, 2NH).^{13}C NMR (DMSO-d_6): δ 12.97, 61.15, 112.85, 121.98, 123.30, 126.44, 127.04, 128.26, 130.24, 131.15, 133.85, 138.42, 144.70, 146.96, 148.59, 151.05, 154.31, 155.73, 157.09, 160.63, 161.92, 164.21, 166.63, 171.74. Anal. for $C_{30}H_{22}N_5O_2SBr$ (596.4): Calcd.: C, 60.41; H, 3.72; N, 11.74; S, 5.38; Br, 13.40. Found: C, 60.63; H, 3.95; N, 11.52; S, 5.25; Br, 13.60%.

4.21. *Ethyl 9-(4-bromophenyl)-4-[2-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)hydrazine]-7-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (12e)*

Yellow crystals from ethanol, m.p. 282–284°C, IR υ (cm^{-1}) 3166, 3120 (2NH), 1726 (CO-ester), 1680 (thiazolone-CO), 1605 (C=N). ^{1}H NMR (DMSO-d_6) δ 0.73–0.76 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.39 (s, 2H, CH_2-thiazolone), 3.82–3.85 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.31–7.66 (m, 9H, Ar–H), 8.09 (s, 1H, $C_{(2)}$–H), 11.80 (s, 1H, NH) and 13.05 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.97, 32.89, 61.16, 99.75, 100.24, 121.97, 123.29, 123.82, 128.36, 130.26, 131.16, 133.21, 138.14, 145.19, 146.98, 151.07, 155.72, 157.06, 161.92, 166.64, 173.08. Anal. for $C_{27}H_{19}N_6O_3SBr$ (619.5): Calcd.: C, 52.35; H, 3.09; N, 13.57; S, 10.35; Br, 12.90. Found: C, 52.10; H, 3.32; N, 13.29; S, 10.68; Br, 12.70%.

4.22. *Ethyl 4-(4-bromophenyl)-2-cyano-3-[(ethoxymethylene)amino]-6-phenylthieno-[2,3-b]pyridine-5-carboxylate (13)*

A solution of **6a** (10 mmol) in acetic anhydride (30 ml) was treated with triethylorthoformate (25 mmol). The reaction mixture was heated under reflux for 3 h and then cooled. The solid product was filtered off and crystallized from ethanol to give **13** as yellow crystals (72%), m.p. 160–162°C, IR υ (cm^{-1}): 2213 (CN), 1728 (CO), 1635 (C = N). Anal. for $C_{26}H_{20}N_3O_3SBr$ (534.4): Calcd.: C, 58.43; H, 3.77; N, 7.86; S, 6.00; Br, 14.95. Found: C, 58.65; H, 3.52; N, 7.61; S, 6.23; Br, 14.70%.

4.23. *Reaction of 6a with formic acid and acetic anhydride*

A solution of **6a** (10 mmol) in formic acid (20 ml) or acetic anhydride (20 ml) was heated under reflux for 3 h and then cooled. The solid product was filtered off and crystallized from ethanol to give **14a** and **b**, respectively.

4.24. *Ethyl 9-(4-bromophenyl)-4-oxo-7-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-8-carboxylate (14a)*

Yellow crystals from ethanol, m.p. 282–284°C, IR υ (cm^{-1}); 3166 (NH), 1723 (CO-ester), 1674 (amidic CO). ^{1}H NMR (DMSO-d_6): δ 0.73–0.80 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.83–3.86 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.20–7.66 (m, 9H, Ar–H), 8.13 (s, 1H, $C_{(2)}$–H) and 12.87 (s, 1H, NH). Anal. for $C_{24}H_{16}N_3O_3SBr$ (506.3): Calcd.: C, 56.93; H, 3.18; N, 8.30; S, 6.33; Br, 15.78. Found: C, 56.70; H, 3.40; N, 8.11; S, 6.55; Br, 15.95%.

4.25. *Ethyl 9-(4-bromophenyl)-2-methyl-4-oxo-7-phenyl-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (14b)*

Yellow crystals from ethanol, m.p. 276°C. IR υ (cm^{-1}); 3265 (NH), 1728 (CO-ester), 1657 (amidic CO), 1601 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.78–0.85 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 2.15 (s, 3H, CH_3), 3.86–3.97 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.34–7.71 (m, 9H, Ar–H), 12.85 (s, 1H, NH). Anal. for $C_{25}H_{18}N_3O_3SBr$ (520.4): Calcd.: C, 57.70; H, 3.49; N, 8.07; S, 6.16; Br, 15.35. Found: C, 57.50; H, 3.30; N, 8.300; S, 6.38; Br, 15.05%.

4.26. *Ethyl 4-anilino-9-(4-bromophenyl)-7-phenyl-2-thioxo-1,2-dihydro-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (17)*

A mixture of compound **6a** (10 mmol) and phenylisothiocyanate (15 mmol) in pyridine (30 ml) was heated under reflux for 6 h and then cooled. The reaction mixture was poured onto ice-cold water and acidified with dil. HCl. The solid product was filtered off and crystallized from ethanol to give compound **17** as yellow crystals (48%), m.p. >360°C. IR υ (cm^{-1}): 3405, 3258 (2NH), 1725 (CO-ester), 1606 (C=N). Anal. for $C_{30}H_{21}N_4O_2S_2Br$ (613.5): Calcd.: C, 58.73; H, 3.45; N, 9.13; S, 10.45; Br, 13.02. Found: C, 58.50; H, 3.66; N, 9.42; S, 10.72; Br, 13.30%.

4.27. *Ethyl 3-amino-8-(4-bromophenyl)-6-phenyl-1H-pyrazolo[3′,4′:4,5]thieno-[2,3-b]pyridine-7-carboxylate (18)*

A solution of **6a** (10 mmol) in hydrazine hydrate (40 ml) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off and crystallized from ethanol to give **18** as orange crystals from ethanol, m.p. 298°C, IR υ (cm^{-1}); 3364, 3332, 3186 (NH_2 and NH), 1724 (CO-ester), 1605 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.71–0.76 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.78–3.81 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 5.25 (s, 2H, NH_2) 7.39–7.76 (m, 9H, Ar–H), 7.99 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.95, 60.96, 111.25, 112.24, 125.32, 128.09, 130.78, 131.21, 133.14, 136.48, 138.68, 141.28, 143.10, 144.58, 151.66, 154.36, 157.97, 166.64, 166.95. Anal. for $C_{23}H_{17}N_4O_2SBr$ (493): Calcd.: C, 55.98; H, 3.45; N, 11.36; S, 6.49; Br, 16.23. Found: C, 55.90; H, 3.40; N, 11.31; S, 6.40; Br, 16.10%.

4.28. *Ethyl 2-(aminocarbonyl)-4-(4-bromophenyl)-3-[(chloroacetyl)amino]-6-phenylthieno[2,3-b]pyridine-5-carboxylate (20)*

A mixture of compound **6c** (10 mmol) and chlorocetylchloride (**19**) (12 mmol) in DMF (30 ml) was stirred at room temperature for 3 h. The reaction mixture was then poured onto ice-cold water. The solid product thus formed was filtered off and crystallized from ethanol to yield compound **20** as yellow crystals (61%), m.p. 246–248°C. IR υ (cm^{-1}): 3467, 3336, 3176 (NH_2 and NH), 1727 (CO-ester), 1673 (CO-amides). ^{1}H NMR (DMSO-d_6): δ 0.67–0.80 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$),

3.76–3.89 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.30 (s, 2H, $COCH_2Cl$), 7.24 (s, 2H, NH_2) 7.34–7.66 (m, 9H, Ar–H) and 13.23 (s, 1H, NH). Anal. for $C_{25}H_{19}N_3O_4SBrCl$ (572.8): Calcd.: C, 52.42; H, 3.34; N, 7.34; S, 5.60; Br, 13.95; Cl, 6.19. Found: C, 52.63; H, 3.67; N, 7.15; S, 5.34; Br, 13.70; Cl, 6.32%.

4.29. *Ethyl 9-(4-bromophenyl)-2-(chloromethyl)-4-oxo-7-phenyl-3,4-dihydro-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (21)*

A solution of **20** (10 mmol) in glacial acetic acid (30 ml) containing 5 ml of acetic anhydride was heated under reflux for 4 h and then cooled. The solid product obtained was filtered off and crystallized from ethanol to give **21** as yellow crystals (70%), m.p. 278–280°C. IR υ (cm^{-1}): 3173 (NH), 1727 (CO-ester), 1652 ($C_{(4)}$=O). ^{1}H NMR (DMSO-d_6): δ 0.78–0.85 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 2.15 (s, 2H, CH_2Cl) 3.86–3.97 (q, $J = 7.0$ Hz, 2H, $\underline{CH_2}CH_3$), 7.346–7.388 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.57–7.58 (m, 5H, Ar–H), 7.668–7.710 (d, $J = 8.4$ Hz, 2H, Ar–H) and 12.85 (s, 1H, NH). Anal. for $C_{25}H_{17}N_3O_3SBrCl$ (554.8): Calcd.: C, 54.12; H, 3.09; N, 7.57; S, 5.78; Br, 14.40; Cl, 6.39. Found: C, 54.33; H, 3.34; N, 7.32; S, 5.60; Br, 14.62; Cl, 6.66%.

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