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Synthesis and characterization of 6-(aryl)-2-thioxo-1,2-dihydropyridine-3-carbonitriles

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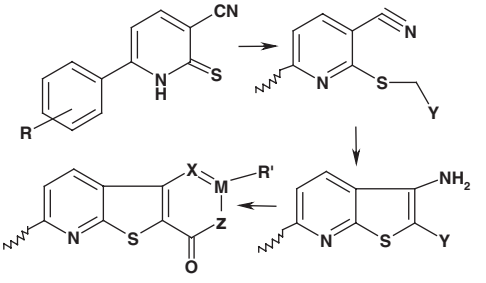
In the present study, 3-aminothieno[2,3-b]pyridines, pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidinones, and pyrido[3′,2′:4,5]thieno[3,2-d][1,3]oxazinones were prepared via the reaction of 6-(aryl)-2-thioxo-1,2-dihydropyridine-3-carbonitriles with active-halogen-containing compounds. The structures of all the newly synthesized heterocyclic compounds were established by considering elemental analysis and spectral data.



Y = CN, $CONH_2$, $COCH_3$, COOH, COAr; X = M = Z = Nitrogen; M = Nitrogen or CarbonR = R' = H, CH_3, Cl

Keywords: thienopyridines; pyridinethiones; pyridothienopyrimidinones; pyridothienotriazines; pyridothienooxazinones

Introduction

In the present study, several new heterocyclic derivatives with a range of biological activities have been obtained. The pyridine nucleus constitutes the major part of these derivatives. Pyridines have been reported earlier to exhibit diverse biological activities as antioxidants and biocides (*1–3*) and

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function as valuable anticancer (*4*) and antimicrobial (*5*) substances. For example, a wide range of antimicrobial (*6–9*), anticancer (*10*), and anti-inflammatory (*11*) biological activities have been attributed specifically to thieno[2,3-b]pyridines. In addition, pyrimidines were reported to exhibit antitumor (*12*), anticancer (*13*), and anti-inflammatory (*14*) activities and were used as new drugs for treatment of insomnia (*15*). In light of all these considerations and in continuation of our long-term interest in the chemistry of pyridines (*16–23*), we were motivated to synthesize and characterize sulfur-containing derivatives of these compounds.

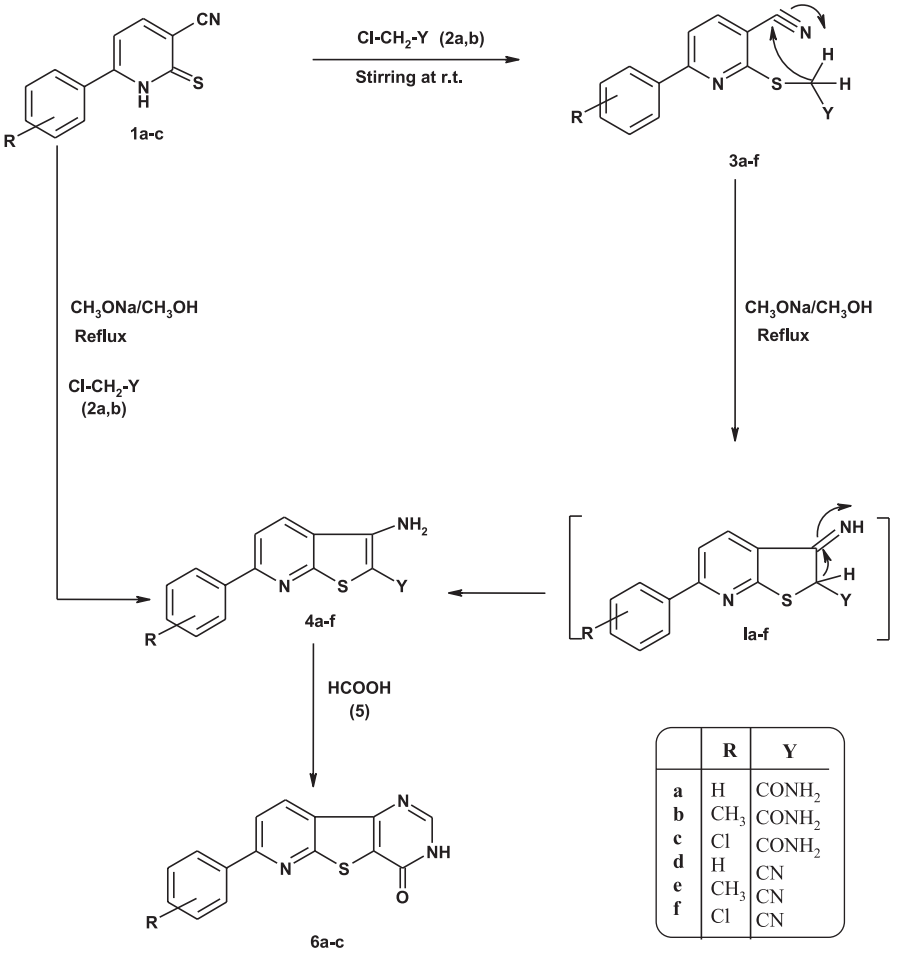
Results and discussion

We were interested in exploring the synthetic potential of 6-(aryl)-2-thioxo-1,2-dihydropyridine-3-carbonitriles **1a–1c** (*24–26*) (R = H, CH_3, and Cl, respectively) as substrates in reactions with active-halogen-containing compounds such as chloroacetamide and chloroacetonitrile (**2a** and **2b**). Thus, we were delighted to find that **1a** reacted with chloroacetamide (**2a**) and chloroacetonitrile (**2b**) in methanolic sodium methoxide under stirring at room temperature for 30 min to give **3a** and **3d**. The IR (cm^{-1}) spectra of these reaction products showed an absorption band for the CN group and exhibited ^{1}H NMR spectra that revealed the signals for $-S-CH_2-$, pyridine, and aromatic protons. Moreover, their mass spectra gave molecular ion peaks (M^+) at $m/z = 269$ and 251, which correspond to the molecular weights of the assigned structures **3a** and **3d**, respectively. A further verification of the structures of **3a** and **3d** was obtained by the detection of peaks at *m/z* corresponding to the loss of the $CONH_2$, CH_2CONH_2, SCH_2CONH_2, CH_2CN, and SCH_2CN fragments (cf. Scheme 1). Similarly, analogs **1b** and **1c** reacted with **2a** and **2b** under the same experimental conditions as **1a** to afford the corresponding products **3b**, **3c**, **3e**, and **3f**, respectively, whose structures were established by the examination of their IR, ^{1}H NMR, and mass spectra and confirmed by elemental analyses (cf. Scheme 1). Further confirmation of the **3a–3f** structures arose from their cyclization in methanolic sodium methoxide under reflux for 5 h to give **4a–4f**, respectively. A CN absorption band was absent in the IR spectra of the cyclization products and instead a band for the newly formed NH_2 was detected.

The work was extended to explore the synthetic potential of **4a–4f** to synthesize a variety of heterocyclic compounds required for several chemical transformations to produce compounds for our medicinal chemistry program. Thus, it has been found that **4a–4c** reacted with formic acid (**5**) to afford the corresponding pyridothienopyrimidinones **6a–6c** whose structures were verified by IR and elemental analyses. In addition, the mass spectra of **6a–6c** gave the parent peaks (M^+) at $m/z = 279$, 293, and 313, which correspond to their molecular weights (cf. Scheme 1).

In a further investigation, compounds **4a–4c** reacted with acetic anhydride (**7**) under reflux for 3–5 h to afford unexpectedly the reaction products **8a–8c**. The IR (cm^{-1}) spectra of these reaction products showed bands corresponding to NH and CO groups. Moreover, the mass spectra of **8a–8c** gave $m/z = 293$, 307, and 327, which correspond to their respective molecular weights. On the other hand, pyridothienotriazines **10a–10c** were obtained in good yields and in a very pure state through the reaction of **4a–4c** with nitrous acid (**9**). The structures of **10a–10c** were elucidated by the examination of their IR (cm^{-1}) spectra, which exhibited absorption bands for both CO and NH groups, and by the examination of their mass spectra, which exhibited the parent peaks at $m/z = 280$, 294, and 314, which correspond to their molecular weights.

The reactivity of both neighboring NH_2 and $CONH_2$ groups in **4a–4c** and NH_2 and CN in **4d–4f** with both phenyl isothiocyanate (**11**) and carbon disulfide (**13**) was examined. Thus, compounds **4d–4f** reacted with phenyl isothiocyanate (**11**) in pyridine (15 ml) under reflux for 6 h to give the reaction products **12a–12c**, respectively. The IR spectra of these reaction products showed no absorption bands for the CN group, and the NH_2 group was not detected in either the IR or ^{1}H NMR spectra. Moreover, their mass spectra gave the parent peaks (M^+) at $m/z = 386$, 400, and

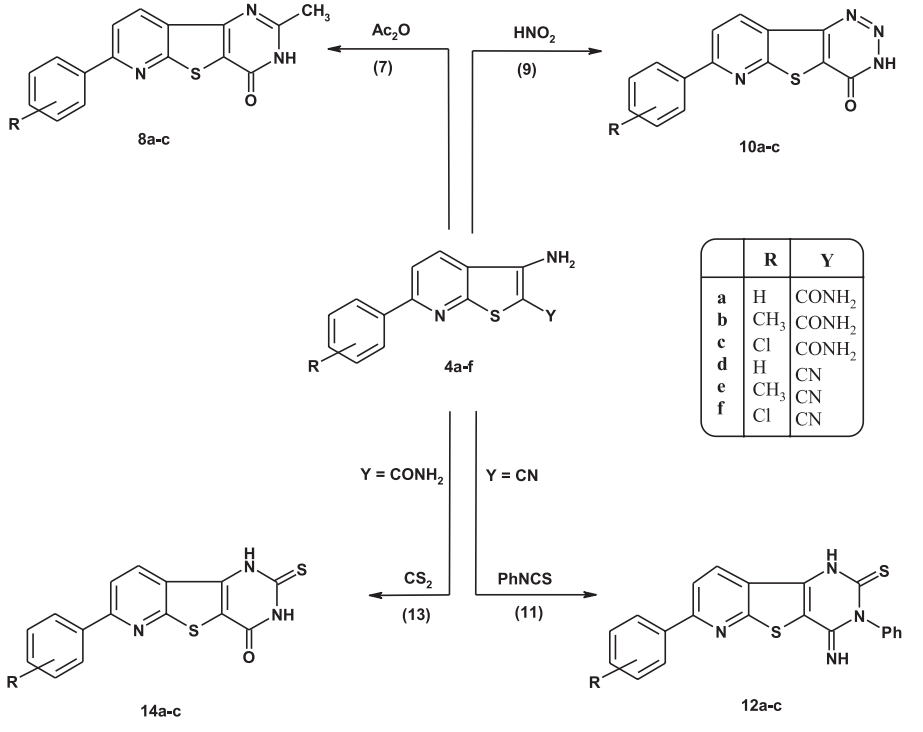


Scheme 1. Synthetic route of compounds **3**, **4**, **6**.

420, which correspond to their molecular weights. Other peaks corresponding to fragment ions at $m/z = 309$, 385, and 325 in the case of compound **12a**; at $m/z = 323$, 399, and 341 in the case of **12b**; and at $m/z = 343$ (M^+-Ph), 342 (M^+-H), and 361 (M^+-HNCS) in the case of **12c** also provide verification of the product structures. Compounds **4a**–**4c** were reacted with carbon disulfide (**13**) in pyridine to give the reaction products **14a**–**14c** whose structures were established by consideration of their IR and ^{1}H NMR data and their elemental analysis. Moreover, their mass spectra gave the parent ions at $m/z = 311$, 325, and 345, which correspond to their molecular weights (cf. Scheme 2).

In a further investigation, **1a**–**1c** reacted with 1-bromo-2-phenylethan-2-one (**15a**) in methanolic sodium methoxide under stirring at room temperature for 15 min to give the corresponding 2-alkylthio derivatives **16a**–**16c** whose structures were elucidated by considering their IR (cm^{-1}) and ^{1}H NMR spectra and their elemental analyses.

The mass spectra of **16a**–**16c** gave the parent peaks (M^+) at $m/z = 302$, 316, and 336, which correspond to their molecular weights (cf. Experimental). In addition, **16a**–**16c** were cyclized in ethanolic sodium ethoxide under reflux for 30 min to give the corresponding thieno[2,3-b]pyridine derivatives **17a**–**17c**, respectively, which were also obtained via refluxing of **1a**–**1c** with **15a**



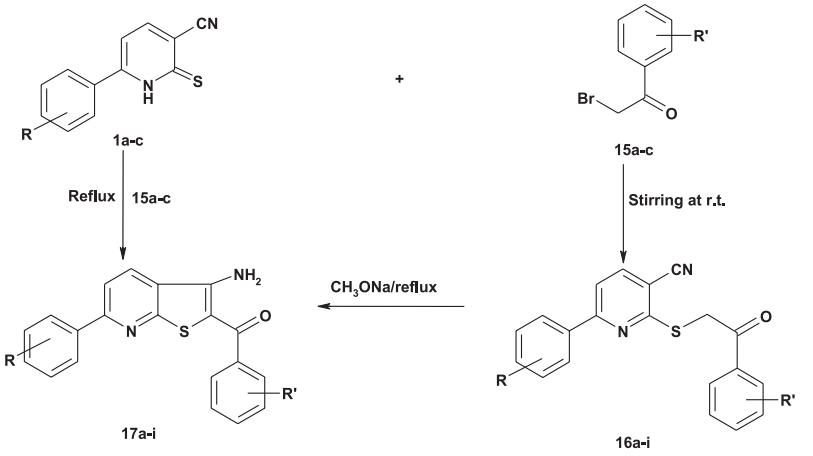
	R	Y
a	H	$CONH_2$
b	CH_3	$CONH_2$
c	Cl	$CONH_2$
d	H	CN
e	CH_3	CN
f	Cl	CN

Scheme 2. Synthetic route of compounds **8**, **10**, **12**, **14**.

in ethanolic sodium ethoxide for 2 h. In similar reactions, **1a–1c** were reacted with **15b** and **15c** in methanolic sodium methoxide under the above-mentioned experimental conditions to give the corresponding 2-alkylthiopyridine derivatives **16d–16i**, respectively, whose structures were established by considering their IR, ^{1}H NMR, and mass spectral data and their elemental analyses. Compounds **16d–16i** cyclized in ethanolic sodium ethoxide under reflux for 30 min to afford the corresponding thieno[2,3-b]pyridines **17d–17i** whose structures were established by the examination of their IR, ^{1}H NMR, and mass spectral data and their elemental analyses. On the other hand, authentic samples of **17d–17i** were obtained directly *via* the reactions of **1a–1c** with **15b** and **15c** in ethanolic sodium ethoxide under reflux for 30 min. It is important to point out here that samples of **17a–17i** obtained by the two pathways were identical in all physical and chemical properties (cf. Scheme 3).

Compounds **1a–1c** also reacted with chloroacetone (**18a**) in methanolic sodium methoxide under stirring for 15 min at room temperature to give the corresponding 2-acetonylthiopyridines **19a–19c**. The IR (cm^{-1}) spectra of these reaction products showed bands for the CN groups, while their ^{1}H NMR spectra revealed the signals for the $-SCH_2-$ protons. Moreover, their mass spectra gave the parent peaks (M^+) at $m/z = 268$, 282, and 302, which correspond to their molecular weights in addition to other peaks at $m/z = M^+-CH_3$, M^+-COCH_3, $M^+-CH_2COCH_3$, and SCH_2COCH_3, which gave further confirmation of their structures. Similarly, compounds **1a–1c** reacted with 3-chloro-2,4-pentandione (**18b**) under the above-mentioned experimental conditions to give the same reaction products **19a–19c** which were obtained from the reactions of **1a–1c** with chloroacetone (**18a**) (Scheme 4).

Compounds **1a–1c** also reacted with ethyl 2-chloro-3-oxobutanoate (**18c**) to give the corresponding thieno[2,3-b]pyridine derivatives **21a–21c** *via* the non-isolable intermediates **19d–19i**.



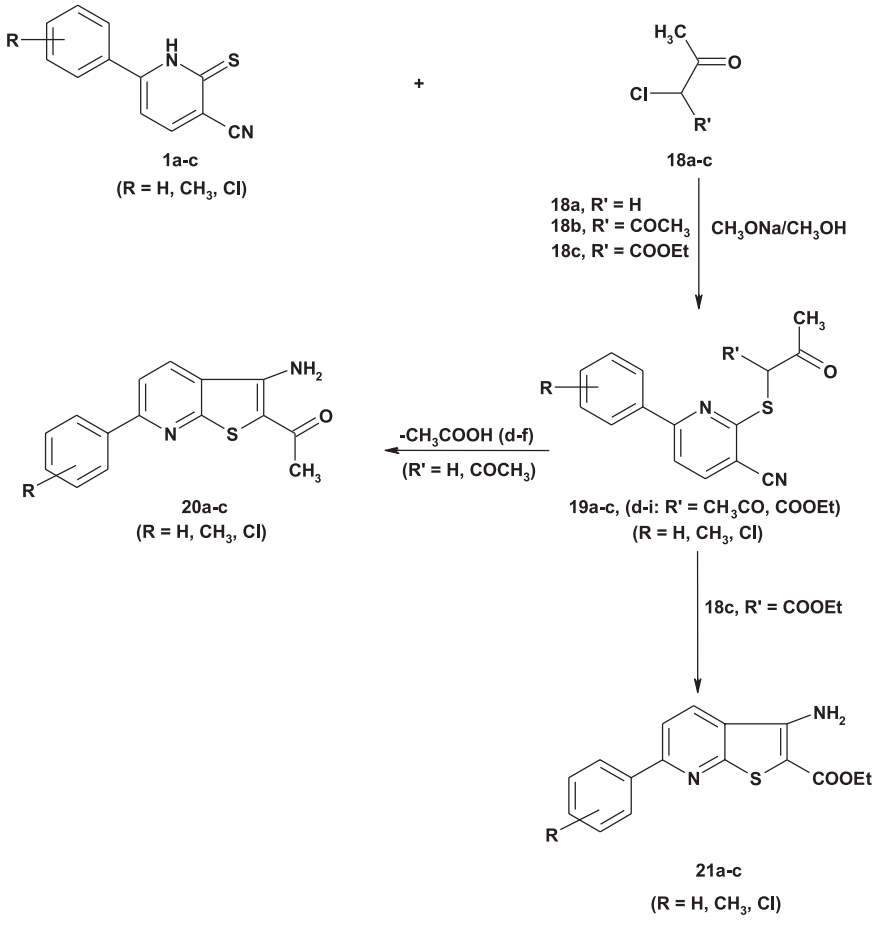
16, 17	R	R'
a	H	H
b	CH_3	H
c	Cl	H
d	H	Cl
e	CH_3	Cl
f	Cl	Cl
g	H	CH_3
h	CH_3	CH_3
i	Cl	CH_3

Scheme 3. Synthetic route of compounds **16**, **17**.

The structures of **21a**–**21c** were confirmed by their IR, ^{1}H NMR, and mass spectral data as well as by their elemental analyses (cf. Experimental). Compounds **1a**–**1c** reacted with chloroacetic acid (**22**) in methanolic sodium methoxide under stirring at room temperature to give the reaction products **23a**–**23c**.

The IR spectra of these reaction products showed absorption bands corresponding to carboxylic CO, OH, and CN groups and their ^{1}H NMR spectra revealed signals for COO*H*, $-CH_2-$, aromatic, and pyridine protons. Moreover, the mass spectra of **23a**–**23c** gave the parent peaks at $m/z = 270$, 284, and 304, which correspond to their molecular weights. The appearance of peaks corresponding to M^+-COOH, M^+-CH_2COOH, and M^+-SCH_2COOH fragments also provides further confirmation of the structures of **23a**–**23c**. Compounds **23a**–**23c** underwent intramolecular cyclization by refluxing in ethanolic sodium ethoxide for 4 h to afford the corresponding thieno[2,3-b]pyridines **24a**–**24c**. The structures of **24a**–**24c** were established by considering the IR and ^{1}H NMR data and by elemental analyses and mass spectrometry.

The synthetic potential of **24a**–**24c** was investigated by examining their reactions with acetic anhydride with the goal of generating a fused oxazine ring on the thieno[2,3-b]pyridine system. The success of the reaction was firmly established by showing that compounds **24a**–**24c** reacted with acetic anhydride to give reaction products in which the absence of COO*H* and NH_2 is clearly demonstrated by the IR and ^{1}H NMR spectral data. Moreover, their mass spectra gave

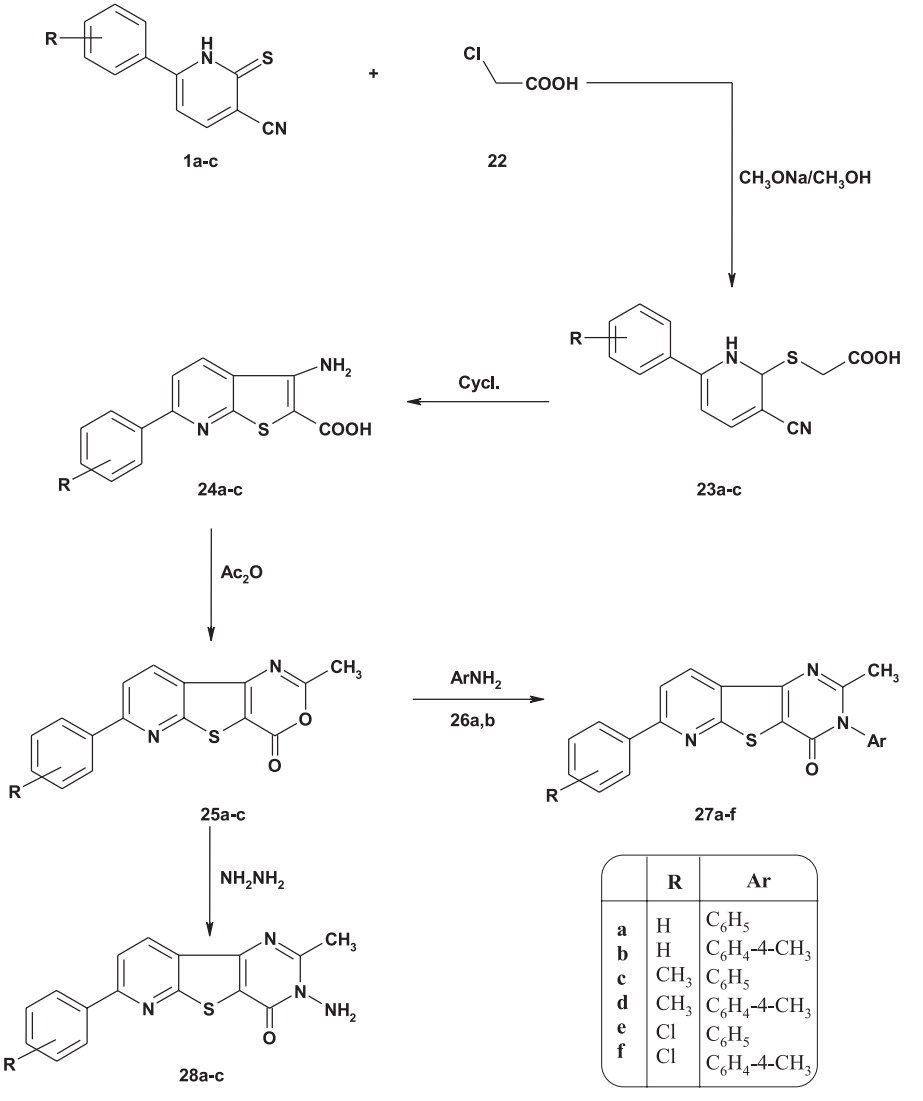


Scheme 4. Synthetic route of compounds **19**, **20**, **21**.

the parent peaks at $m/z = 294$, 308, and 328 corresponding to the molecular weights of **25a**–**25c**. Compounds **25a**–**25c** reacted with aromatic amines **26a** and **26b** and hydrazine to give the pyrimidinones **27a**–**27f** and **28a**–**28c**, respectively, whose structures were elucidated by their IR, ^{1}H NMR, and elemental analysis data. Moreover, their mass spectra gave the parent peaks at 369, 383, 403, 383, 397, 417, 308, 322, and 342 corresponding to the molecular weights of **27a**–**27f** and **28a**–**28c** (cf. Scheme 5).

Conclusion

Both the $-CH_2-$ and CN groups in compounds **3a**–**3f** were involved in the cyclization step to give the imino derivatives **Ia**–**If** as intermediates, which tautomerized to afford the final isolable products **4a**–**4f**, respectively, as illustrated by Scheme 1. During the preparation of compounds **6a**–**6c**, **8a**–**8c**, and **10a**–**10c**, each of formic acid, acetic anhydride, and nitrous acid caused partial hydrolysis of the CN groups at the 2-position of **4d**–**4f** and the products subsequently underwent intramolecular cyclization to give the final isolated reaction products **6a**–**6c**, **8a**–**8c**, and **10a**–**10c**, respectively.



	R	Ar
a	H	C_6H_5
b	H	C_6H_4-4-CH_3
c	CH_3	C_6H_5
d	CH_3	C_6H_4-4-CH_3
e	Cl	C_6H_5
f	Cl	C_6H_4-4-CH_3

Scheme 5. Synthetic route of compounds **23**, **24**, **25**, **27**, **28**.

Biological activity

The antimicrobial and antifungal properties of all the newly synthesized heterocyclic compounds were tested. Some of these compounds exhibited high activities and, on the other hand, other compounds exhibited low, medium, or no activities (cf. Table 1).

Experimental

All melting points are uncorrected. IR spectra (KBr discs) were recorded on Shimadzu FTIR-8201PC spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury 300 MHz spectrometers using TMS as an internal standard and DMSO-d_6 as a solvent, and chemical shifts, δ, are expressed in ppm. Mass spectra were recorded on a GCMS-QP1000EX spectrometer

Table 1. Response of various microorganisms to some synthesized compounds *in vitro*.

Compound	Inhibition zone diameter (mm/mg sample)			
	Escherichia coli (G^-)	*Staphylococcus aureus* (G^+)	*Aspergillus flavus* (fungus)	*Candida albicans* (fungus)
Tetracycline (antibacterial agent)	33	30	–	–
Amphotericin B (antifungal agent)	–	–	19	20
4a	13	10	9	9
4b	13	13	7	0
4c	12	11	11	9
4d	14	12	9	10
4e	12	15	5	7
4f	11	14	8	11
8a	16	15	0	0
8b	15	14	11	9
8c	14	13	9	10
12a	12	11	8	10
12b	20	25	11	14
12c	16	15	11	9
14a	12	12	0	0
14b	13	12	11	0
14c	14	13	9	0
16a	14	12	10	9
16b	13	15	12	11
16c	15	11	7	8
16d	11	15	9	11
16e	15	13	11	10
16f	14	16	9	11
16g	15	14	8	10
16h	13	15	8	11
16i	16	12	9	10
23a	14	13	12	9
23b	15	13	9	11
23c	13	12	11	7
27a	14	13	11	9
27b	11	15	10	11
27c	14	12	9	10
28a	13	11	9	10
28b	15	14	12	11
28c	11	15	9	10

using inlet type at 70 eV. Microanalyses were performed at the Micro-analytical Center of Cairo University.

Compounds **1a–1c** were prepared according to the literature procedure (*24–26*).

Synthesis of 3a–3f, 16a–16i, 19a–19c, and 23a–23c (general method)

A solution of each of **1a–1c** (0.63, 0.67, and 0.73 g, 3 mmol) and 2-chloroacetamide (**2a**, 0.28 g, 3 mmol), chloroacetonitrile (**2b**, 0.22 g, 3 mmol), 2-bromo-1-phenylethanone (**15a**, 0.59 g), 2-bromo-1-(4-chlorophenyl)ethanone (**15b**, 0.69 g), 2-bromo-1-(4-methylphenyl)ethanone (**15c**, 0.63 g) (3 mmol from each), 1-chloroacetone (**18a**, 0.27 g, 3 mmol), 3-chloropentane-2,4-dione (**18b**, 0.40 g, 3 mmol), 2-chloro-3-oxobutanoate (**18c**, 0.49 g, 3 mmol), and chloroacetic acid (**22**, 0.28 g, 3 mmol) in sodium methoxide (prepared from 0.07 g of sodium metal and 25 ml methanol) was stirred at room temperature for 15 min. The precipitates that were formed were collected by filtration, washed with water, and crystallized from the proper solvent to afford **3a–3f**, **16a–16i**, **19a–19c**, and **23a–23c**, respectively.

2-[(3-Cyano-6-phenylpyridin-2-yl)sulfanyl]acetamide (3a)

Yellow crystals (67%), crystallized from dioxane, mp. 255°C, IR (ν, cm^{-1}): 2976, 2877 (C−H stretching of aliphatic), 3422, 3299 (NH_2), 3067 (C−H aromatic), 2219 (CN), 1669 (amide CO); MS (m/z) = 269 (M^+, 100%, which corresponds to its molecular weight), 268 (M^+−H, 13.8%), 267 (M^+−2H, 9.4%), 253 (M^+−NH_2, 32.8%), 225 (M^+−$CONH_2$, 17.2%), 211 (M^+−CH_2CONH_2, 22.1%), 179 (M^+−SCH_2CONH_2, 52.2%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.52 (s, 2H, −SCH_2−), 5.58 (br., s, 2H, −NH_2), 7.02–8.44 (m, 5H, Ar, pyridinyl C_4H), 9.57 (s, 2H, pyridinyl C_5H). Anal. for $C_{14}H_{11}N_3OS$ (269), calcd./found (%): C (62.43/62.45), H (4.12/4.15), N (15.60/15.58), and S (11.91/11.88).

2-{[3-Cyano-6-(4-methylphenyl)pyridin-2-yl]sulfanyl}acetamide (3b)

Brown crystals (58%), crystallized from dioxane, mp. 230°C, IR (ν, cm^{-1}): 2977, 2873 (C−H stretching of aliphatic), 3417, 3276 (NH_2), 3086 (C−H aromatic), 2222 (CN), 1673 (amide CO); MS (m/z) = 283 (M^+, 100%, which corresponds to its molecular weight), 382 (M^+−H, 22.3%), 281 (M^+−2H, 13.2%), 267 (M^+−NH_2, 17.3%), 239 (M^+−$CONH_2$, 33.8%), 225 (M^+−CH_2CONH_2, 15.9%), 193 (M^+−SCH_2CONH_2, 57.9%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 0.89 (s, 3H, CH_3), 4.24 (s, 2H, −SCH_2−), 5.56 (br., s, 2H, −NH_2), 7.15–8.53 (m, 5H, Ar, pyridinyl C_4H), 9.68 (s, 1H, pyridinyl C_5H). Anal. for $C_{15}H_{13}N_3OS$ (283), calcd./found (%): C (63.58/63.61), H (4.62/4.59), N (14.83/14.80), and S (11.32/11.29).

2-{[6-(4-Chlorophenyl)-3-cyanopyridin-2-yl]sulfanyl}acetamide (3c)

Yellow crystals (60%), crystallized from dioxane, mp. 235°C, IR (ν, cm^{-1}): 2977, 2873 (C−H stretching of aliphatic), 3417, 3276 (NH_2), 3086 (C−H aromatic), 2222 (CN), 1673 (amide CO); MS (m/z) = 303 (M^+, 100%, which corresponds to its molecular weight), 302 (M^+−H, 17.3%), 301 (M^+−2H, 22.6%), 287 (M^+−NH_2, 31.2%), 259 (M^+−$CONH_2$, 23.5%), 245 (M^+−CH_2CONH_2, 52.3%), 213 (M^+−SCH_2CONH_2, 22.3%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.35 (s, 2H, −SCH_2−), 5.67 (br., s, 2H, −NH_2), 7.13–8.42 (m, 5H, Ar, pyridinyl C_4H), 9.56 (s, 1H, pyridinyl C_5H). Anal. for $C_{14}H_{10}ClN_3OS$ (303), calcd./found (%): C (55.35/55.32), H (3.32/3.29), Cl (11.67/11.69), N (13.83/13.85), and S (10.56/10.58).

2-[(Cyanomethyl)sulfanyl]-6-phenylpyridine-3-carbonitrile (3d)

Brown crystals (80%), crystallized from dioxane, mp. 265°C, IR (ν, cm^{-1}): 2985, 2873 (C−H stretching of aliphatic), 3076 (C−*H*, aromatic), 2219 (CN); MS (m/z) = 251 (M^+, 100%, which corresponds to its molecular weight), 225 (M^+−CN, 21.7%), 211 (M^+−CH_2CN, 37.6%), 179 (M^+−SCH_2CN, 57.9%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.55 (s, 2H, −SCH_2−), 7.11–8.70 (m, 6H, Ar, pyridinyl C_5H), 9.51 (s, 1H, pyridinyl C_4H). Anal. for $C_{14}H_9N_3S$ (251), calcd./found (%): C (66.91/66.89), H (3.61/3.58), N (16.72/16.75), and S (12.76/12.78).

2-[(Cyanomethyl)sulfanyl]-6-(4-methylphenyl)pyridine-3-carbonitrile (3e)

Yellow crystals (70%), crystallized from ethanol, mp. 220°C, IR (ν, cm^{-1}): 2987, 2879 (C−H stretching of aliphatic), 3083 (C−*H*, aromatic), 2220 (CN); MS (m/z) = 265 (M^+, 100%, which corresponds to its molecular weight), 239 (M^+−CN, 14.5%), 225 (M^+−CH_2CN, 19.3%), 193 (M^+−SCH_2CN, 44.3%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.00 (s, 3H, CH_3), 4.38 (s, 2H, −SCH_2−), 7.22–8.51 (m, 5H, Ar, pyridinyl C_5H), 9.50 (s, 1H, pyridinyl C_4H). Anal. for

$C_{15}H_{11}N_3S$ (265), calcd./found (%): C (67.90/67.92), H (4.18/4.15), N (15.84/15.81), and S (12.08/12.11).

6-(4-Chlorophenyl)-2-[(cyanomethyl)sulfanyl]pyridine-3-carbonitrile (3f)

Brown crystals (60%), crystallized from ethanol, mp. 185°C, IR (ν, cm^{-1}): 2979, 2895 (C−H stretching of aliphatic), 3068 (C−*H*, aromatic), 2217 (CN); MS (m/z) = 285 (M^+, 100%, which corresponds to its molecular weight), 284 (M^+−H, 13.9%), 283 (M^+−2H, 23.7%), 269 (M^+-NH_2, 17.2%), 255 ($M^+-CH_2NH_2$, 44.3%), 223 ($M^+-SCH_2NH_2$, 27.1%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.63 (s, 2H, $-SCH_2-$), 7.14–8.52 (m, 5H, Ar, pyridinyl C_5H), 9.62 (s, 1H, pyridinyl C_4H). Anal. for $C_{14}H_8ClN_3S$ (285), calcd./found (%): C (58.84/58.87), H (2.82/2.85), Cl (12.41/12.39), N (14.71/14.69), and S (11.22/11.25).

2-[(2-Oxo-2-phenylethyl)thio]-6-phenylpyridine-3-carbonitrile (16a)

Brown crystals (56%), crystallized from ethanol, mp. 225°C, IR (ν, cm^{-1}): 2985, 2879 (C−H stretching of aliphatic), 3087 (C−*H*, aromatic), 2219 (CN), 1704 (CO); MS (m/z) = 330 (M^+, 65.3%, which corresponds to its molecular weight), 225 (M^+−COPh, 37.5%), 211 (M^+-CH_2COPh, 75.2%), 179 (M^+-SCH_2COPh, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.29 (s, 2H, $-SCH_2-$), 7.15–8.83 (m, 11H, Ar, pyridinyl C_5H), 9.53 (s, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{14}N_2OS$ (330), calcd./found (%): C (72.70/72.67), H (4.27/4.29), N (8.48/8.51), and S (9.71/9.74).

2-[(2-Oxo-2-phenylethyl)thio]-6-(4-methylphenyl)pyridine-3-carbonitrile (16b)

Yellow crystals (77%), crystallized from ethanol, mp. 199°C, IR (ν, cm^{-1}): 2979, 2885 (C−H stretching of aliphatic), 3067 (C−*H*, aromatic), 2220 (CN), 1701 (CO); MS (m/z) = 344 (M^+, 53.8%, which corresponds to its molecular weight), 253 (M^+−COPh, 32.8%), 239 (M^+-CH_2COPh, 88.5%), 207 (M^+-SCH_2CO Ph, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.13 (s, 3H, CH_3), 4.16 (s, 2H, $-SCH_2-$), 7.28–8.91 (m, 10H, Ar, pyridinyl C_5H), 9.48 (s, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{16}N_2OS$ (344), calcd./found (%): C (73.23/73.25), H (4.68/4.71), N (8.13/8.16), and S (9.31/9.34).

2-[(2-Oxo-2-phenylethyl)thio]-6-(4-chlorophenyl)pyridine-3-carbonitrile (16c)

Yellow crystals (70%), crystallized from dioxane, mp. 259°C, IR (ν, cm^{-1}): 2973, 2889 (C−H stretching of aliphatic), 3085 (C−*H*, aromatic), 2216 (CN), 1700 (CO); MS (m/z) = 364 (M^+, 47.3%, which corresponds to its molecular weight), 293 (M^+−COPh, 17.3%), 279 (M^+-CH_2COPh, 75.9%), 247 (M^+-SCH_2COPh, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 4.24 (s, 2H, $-SCH_2-$), 7.16–8.78 (m, 10H, Ar, pyridinyl C_5H), 9.63 (s, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{13}ClN_2OS$ (364), calcd./found (%): C (65.84/65.87), H (3.59/3.61), Cl (9.72/9.69), N (7.68/7.66), and S (8.79/8.81).

2-{[2-(4-Chlorophenyl)-2-oxoethyl]thio}-6-phenylpyridine-3-carbonitrile (16d)

Yellow crystals (55%), crystallized from ethanol, mp. 165°C, IR (ν, cm^{-1}): 2955, 2869 (C−H stretching of aliphatic), 3069 (C−*H*, aromatic), 2217 (CN), 1705 (CO); MS (m/z) = 364 (M^+, 64.1%, which corresponds to the molecular weight), 259 (M^+−COPh, 28.3%), 245

(M^+-CH_2COPh, 66.9%), 213 (M^+-SCH_2COPh, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 4.23 (s, 2H, $-SCH_2-$), 7.15–8.85 (m, 10H, Ar, pyridinyl C_5H), 9.56 (s, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{13}ClN_2OS$ (364), calcd./found (%): C (65.84/65.87), H (3.59/3.61), Cl (9.72/9.69), N (7.68/7.66), and S (8.79/8.81).

2-{[2-(4-Chlorophenyl)-2-oxoethyl]thio}-6-(4-methylphenyl)pyridine-3-carbonitrile (16e)

Brown crystals (82%), crystallized from ethanol, mp. 180°C, IR (ν, cm^{-1}): 2959, 2872 (C−H stretching of aliphatic), 3074 (C−*H*, aromatic), 2222 (CN), 1700 (CO); MS (m/z) = 378 (M^+, 44.3%, which corresponds to its molecular weight), 273 ($M^+-COC_6H_4-p\text{-}CH_3$, 21.8%), 259 ($M^+-CH_2COC_6H_4-p\text{-}CH_3$, 67.2%), 227 ($M^+-SCH_2COC_6H_4-p\text{-}CH_3$, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.02 (s, 3H, CH_3), 4.16 (s, 2H, $-SCH_2-$), 7.13–8.83 (m, 9H, Ar, pyridinyl C_5H), 9.56 (s, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{15}ClN_2OS$ (378), calcd./found (%): C (66.57/66.59), H (3.99/4.02), Cl (9.36/9.33), N (7.39/7.41), and S (8.46/8.48).

2-{[2-(4-Chlorophenyl)-2-oxoethyl]thio}-6-(4-chlorophenyl)pyridine-3-carbonitrile (16f)

Brown crystals (50%), crystallized from ethanol, mp. 188°C, IR (ν, cm^{-1}): 2967, 2869 (C−H stretching of aliphatic), 3076 (C−*H*, aromatic), 2221 (CN), 1702 (CO); MS (m/z) = 399 (M^+, 53.8%, which corresponds to its molecular weight), 260 ($M^+-COC_6H_4-p\text{-}Cl$, 18.3%), 246 ($M^+-CH_2COC_6H_4-p\text{-}Cl$, 55.9%), 214 ($M^+-SCH_2COC_6H_4-p\text{-}Cl$, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 4.26 (s, 2H, $-SCH_2-$), 7.10–8.84 (m, 9H, Ar, pyridinyl C_5H), 9.44 (s, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{12}Cl_2N_2OS$ (399), calcd./found (%): C (60.16/60.18), H (3.03/3.05), Cl (17.76/17.74), N (7.02/6.99), and S (8.03/8.00).

2-{[2-(4-Methylphenyl)-2-oxoethyl]thio}-6-phenylpyridine-3-carbonitrile (16g)

Yellow crystals (83%), crystallized from ethanol, mp. 215°C, IR (ν, cm^{-1}): 2971, 2892 (C−H stretching of aliphatic), 3076 (C−*H*, aromatic), 2218 (CN), 1700 (CO); MS (m/z) = 344 (M^+, 53.8%, which corresponds to the molecular weight), 239 ($M^+-COC_6H_4-p\text{-}CH_3$, 32.8%), 225 ($M^+-CH_2COC_6H_4-p\text{-}CH_3$, 88.5%), 193 ($M^+-SCH_2CO\ C_6H_4-p\text{-}CH_3$, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.13 (s, 3H, CH_3), 4.16 (s, 2H, $-SCH_2-$), 7.28–8.91 (m, 10H, Ar, pyridinyl C_5H), 9.48 (s, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{16}N_2OS$ (344), calcd./found (%): C (73.23/73.25), H (4.68/4.71), N (8.13/8.16), and S (9.31/9.34).

2-{[2-(4-Methylphenyl)-2-oxoethyl]thio}-6-(4-methylphenyl)pyridine-3-carbonitrile (16h)

Yellow crystals (59%), crystallized from ethanol, mp. 126°C, IR (ν, cm^{-1}): 2979, 2898 (C−H stretching of aliphatic), 3088 (C−*H*, aromatic), 2216 (CN), 1705 (CO); MS (m/z) = 358 (M^+, 43.6%, which corresponds to the molecular weight), 253 ($M^+-COC_6H_4-p\text{-}CH_3$, 18.5%), 239 ($M^+-CH_2COC_6H_4-p\text{-}CH_3$, 75.8%), 207 ($M^+-SCH_2CO\ C_6H_4-p\text{-}CH_3$, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.13 (s, 6H, two CH_3), 4.26 (s, 2H, $-SCH_2-$), 7.13–8.84 (m, 9H, Ar, pyridinyl C_5H), 9.57 (s, 1H, pyridinyl C_4H). Anal. for $C_{22}H_{18}N_2OS$ (358), calcd./found (%): C (73.71/73.69), H (5.06/5.09), N (7.82/7.85), and S (8.95/8.97).

2-{[2-(4-Methylphenyl)-2-oxoethyl]thio}-6-(4-chlorophenyl)pyridine-3-carbonitrile (16i)

Brown crystals (68%), crystallized from ethanol, mp. 150°C, IR (ν, cm^{-1}): 2968, 2877 (C−H stretching of aliphatic), 3085 (C−*H*, aromatic), 2217 (CN), 1700 (CO); MS (m/z) = 378 (M^+, 54.8%, which corresponds to the molecular weight), 273 ($M^+-COC_6H_4-p\text{-}CH_3$, 33.6%), 259 ($M^+-CH_2COC_6H_4-p\text{-}CH_3$, 73.4%), 227 ($M^+-SCH_2CO\ C_6H_4-p\text{-}CH_3$, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.11 (s, 3H, CH_3), 4.35 (s, 2H, $-SCH_2-$), 7.11–8.81 (m, 9H, Ar, pyridinyl C_5H), 9.63 (s, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{15}ClN_2OS$ (378), calcd./found (%): C (66.57/66.59), H (3.99/4.02), Cl (9.36/9.33), N (7.39/7.41), and S (8.46/8.48).

2-[(2-Oxopropyl)sulfanyl]-6-phenylpyridine-3-carbonitrile (19a)

Yellow crystals (58%), mp. 195°C, crystallized from ethanol, IR (ν, cm^{-1}): 2960, 2879 (C−H stretching of aliphatic), 3082 (C−*H*, aromatic), 2218 (CN), 1700 (CO); MS (m/z) = 268 (M^+, 48.5%, which corresponds to its molecular weight), 225 (M^+-COCH_3, 58.2%), 211 ($M^+-CH_2COCH_3$, 52.1%), 179 ($M^+-SCH_2COCH_3$, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.67 (s, 3H, CH_3CO), 4.26 (s, 2H, $-SCH_2-$), 7.15–8.83 (m, 6H, Ar, pyridinyl C_5H), 9.66 (s, 1H, pyridinyl C_4H). Anal. for $C_{15}H_{12}N_2OS$ (268), calcd./found (%): C (67.14/67.16), H (4.51/4.53), N (10.44/10.47), and S (11.95/11.98).

6-(4-Methylphenyl)-2-[(2-oxopropyl)sulfanyl]pyridine-3-carbonitrile (19b)

Yellow crystals (65%), 225°C, crystallized from ethanol, IR (ν, cm^{-1}): 2978, 2898 (C−H stretching of aliphatic), 3076 (C−*H*, aromatic), 2222 (CN), 1708 (CO); MS (m/z) = 282 (M^+, 65.2%, which corresponds to its molecular weight), 239 (M^+-COCH_3, 55.8%), 225 ($M^+-CH_2COCH_3$, 52.1%), 193 ($M^+-SCH_2COCH_3$, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.35 (s, 3H, CH_3), 2.67 (s, 3H, CH_3CO), 4.26 (s, 2H, $-SCH_2-$), 7.16–8.88 (m, 5H, Ar, pyridinyl C_5H), 9.68 (s, 1H, pyridinyl C_4H). Anal. for $C_{16}H_{14}N_2OS$ (282), calcd./found (%): C (68.06/68.03), H (5.00/4.97), N (9.92/9.95), and S (11.36/11.34).

6-(4-Chlorophenyl)-2-[(2-oxopropyl)sulfanyl]pyridine-3-carbonitrile (19c)

Yellow crystals (75%), 263°C, crystallized from ethanol, IR (ν, cm^{-1}): 2973, 2891 (C−H stretching of aliphatic), 3066 (C−*H*, aromatic), 2218 (CN), 1705 (CO); MS (m/z) = 302 (M^+, 66.3%, which corresponds to its molecular weight), 259 (M^+-COCH_3, 58.2%), 245 ($M^+-CH_2COCH_3$, 52.1%), 213 ($M^+-SCH_2COCH_3$, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.53 (s, 3H, CH_3CO), 4.17 (s, 2H, $-SCH_2-$), 7.10–8.90 (m, 5H, Ar, pyridinyl C_5H), 9.66 (s, 1H, pyridinyl C_4H). Anal. for $C_{15}H_{11}ClN_2OS$ (302), calcd./found (%): C (59.50/59.52), H (3.66/3.68), Cl (11.71/11.74), N (9.25/9.27), and S (10.59/10.61).

[(3-Cyano-6-phenylpyridin-2-yl)sulfanyl]acetic acid (23a)

Yellow crystals (52%), crystallized from ethanol, mp. 173°C, IR (ν, cm^{-1}): 2976, 2889 (C−H stretching of aliphatic), 3325–3543 (broad band for acidic OH), 3064 (C−H aromatic), 2215 (CN), 1710 (CO); MS (m/z) = 270 (M^+, 100%, which corresponds to its molecular weight), 253 (M^+-OH, 13.8%), 225 (M^+-COOH, 33.6%), 211 (M^+-CH_2COOH, 17.3%), 179 (M^+-SCH_2COOH, 56.8%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.53 (s, 2H, $-SCH_2-$), 7.12–8.51 (m, 6H, Ar, pyridinyl C_5H), 9.33 (s, 1H, pyridine C_4H), and 13.82 (s, br., 1H, COOH). Anal. for

$C_{14}H_{10}N_2O_2S$ (270), calcd./found (%): C (62.21/62.18), H (3.73/3.71), N (10.36/10.39), and S (11.86/11.84).

{[3-Cyano-6-(4-methylphenyl)pyridin-2-yl]sulfanyl}acetic acid (23b)

Brown crystals (59%), crystallized from ethanol, mp. 185°C, IR (ν, cm^{-1}): 2966, 2896 (C−H stretching of aliphatic), 3318–3522 (broad band for acidic OH), 3069 (C−H aromatic), 2219 (CN), 1708 (CO); MS (m/z) = 284 (M^+, 100%, which corresponds to its molecular weight), 267 (M^+−OH, 23.8%), 239 (M^+−COOH, 39.6%), 225 (M^+−CH_2COOH, 27.8%), 193 (M^+−SCH_2COOH, 53.2%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.10 (s, 3H, CH_3), 2.54 (s, 2H, −SCH_2−), 7.13–8.52 (m, 5H, Ar, pyridinyl C_5H), 9.34 (s, 1H, pyridine C_4H), and 13.57 (s, br., 1H, COOH). Anal. for $C_{15}H_{12}N_2O_2S$ (284), calcd./found (%): C (63.36/63.38), H (4.25/4.28), N (9.85/9.82), and S (11.28/11.31).

{[6-(4-Chlorophenyl)-3-cyanopyridin-2-yl]sulfanyl}acetic acid (23c)

Yellow crystals (66%), crystallized from ethanol, mp. 216°C, IR (ν, cm^{-1}): 2976, 2898 (C−H stretching of aliphatic), 3322–3538 (broad band for acidic OH), 3077 (C−H aromatic), 2222 (CN), 1710 (CO); MS (m/z) = 304 (M^+, 100%, which corresponds to its molecular weight), 287 (M^+−OH, 33.2%), 259 (M^+−COOH, 17.6%), 245 (M^+−CH_2COOH, 38.8%), 213 (M^+−SCH_2COOH, 57.8%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.54 (s, 2H, −SCH_2−), 7.15–8.57 (m, 5H, Ar, pyridinyl C_5H), 9.53 (s, 1H, pyridine C_4H), and 13.62 (s, br., 1H, COOH). Anal. for $C_{14}H_9ClN_2O_2S$ (304), calcd./found (%): C (55.18/55.16), H (2.98/3.01), Cl (11.63/11.65), N (9.19/9.22), and S (10.52/10.55).

Synthesis of 4a–4f, 17a–17i, 20a–20c, and 24a–24c (general method)

A solution of each of **3a**–**3f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol), **16a**–**16i** (0.99, 1.03, 1.09, 1.03, 1.07, 1.13, 1.09, 1.13, and 1.19 g, 3 mmol), **19a**–**19c** (0.80, 0.85, and 0.91 g, 3 mmol), or **23a**–**23c** (0.81, 0.85, and 0.91 g, 3 mmol) in sodium ethoxide solution (prepared from 0.07 g of 3 mmol sodium and 25 ml ethanol) was heated under reflux for 3 h. The solids that formed after cooling were collected by filtration and washed with water and ethanol and then crystallized from dioxane to give **4a**–**4c**, **17a**–**17i**, **20a**–**20c**, and **24a**–**24c**, respectively.

3-Amino-6-phenylthieno[2,3-b]pyridine-2-carbonitrile (4a)

Gray crystals (83%), crystallized from ethanol, mp. 220°C, IR (ν, cm^{-1}): 3412, 3387, 3255, 3165 (NH_2 and amidic NH_2), 1669 (amide CO); MS (m/z) = 251 (M^+, 100%, which corresponds to the molecular weight), 235 (M^+−NH_2, 23.8%), 234 (M^+−NH_2, −H, 18.3%), 233 (M^+−NH_2, −2H, 22.7%), 205 (M^+−$CONH_2$, −2H, 30.9%). Anal. for $C_{14}H_9N_3S$ (251), calcd./found (%): C (66.91/66.89), H (3.61/3.58), N (16.72/16.75), and S (12.76/12.78).

3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridine-2-carbonitrile (4b)

Yellow crystals (55%), crystallized from dioxane, mp. 248°C, IR (ν, cm^{-1}): 2977, 2876 (C−H stretching of aliphatic), 3412, 3345, 3222, 3172 (NH_2 and amidic NH_2), 1672 (amide CO); MS (m/z) = 265 (M^+, 100%, which corresponds to the molecular weight), 249 (M^+−NH_2, 9.9%), 248 (M^+−NH_2, −H, 22.1%), 247 (M^+−NH_2, −2H, 17.5%), 219 (M^+−$CONH_2$, −2H, 18.1%).

Anal. for $C_{15}H_{11}N_3S$ (265), calcd./found (%): C (67.90/67.92), H (4.18/4.15), N (15.84/15.81), and S (12.08/12.11).

3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridine-2-carbonitrile (4c)

Yellow crystals (74%), crystallized from dioxane, mp. 244°C, IR (ν, cm^{-1}): 3401, 3385, 3208, 3185 (NH_2 and amidic NH_2), 1669 (amide CO); MS (m/z) = 285 (M^+, 100%, which corresponds to the molecular weight), 269 (M^+-NH_2, 15.4%), 268 (M^+-NH_2, −H, 23.9%), 267 (M^+-NH_2, −2H, 14.6%), 239 (M^+-CONH_2, −2H, 22.6%). Anal. for $C_{14}H_8ClN_3S$ (285), calcd./found (%): C (58.84/58.87), H (2.82/2.85), Cl (12.41/12.39), N (14.71/14.69), and S (11.22/11.25).

3-Amino-6-phenylthieno[2,3-b]pyridine-2-carboxamide (4d)

Yellow crystals (90%), crystallized from dioxane, mp. 269°C, IR (ν, cm^{-1}): 3464, 3421, 3298, 3158 (NH_2 and amidic NH_2), 1667 (amide CO); MS (m/z) = 269 (M^+, 100%, which corresponds to the molecular weight), 253 (M^+-NH_2, 17.3%), 252 (M^+-NH_2, −H, 44.2%), 251 (M^+-NH_2, −2H, 13.6%), 225 (M^+-CONH_2, −2H, 72.3%), 166 ($M^+-PhCN-NH_2$, 7.3%). Anal. for $C_{14}H_{11}N_3OS$ (269), calcd./found (%): C (62.43/62.45), H (4.12/4.15), N (15.60/15.58), and S (11.91/11.88).

3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridine-2-carboxamide (4e)

Yellow crystals (60%), crystallized from dioxane, mp. 232°C, IR (ν, cm^{-1}): 2987, 2874 (C−H stretching of aliphatic), 3455, 3414, 3277, 3147 (NH_2 and amidic NH_2), 1675 (amide CO); MS (m/z) = 283 (M^+, 100%, which corresponds to the molecular weight), 267 (M^+-NH_2, 23.8%), 266 (M^+-NH_2, −H, 36.3%), 265 (M^+-NH_2, −2H, 21.7%), 237 (M^+-CONH_2, −2H, 56.9%). Anal. for $C_{15}H_{13}N_3OS$ (283), calcd./found (%): C (63.58/63.61), H (4.62/4.59), N (14.83/14.80), and S (11.32/11.29).

3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridine-2-carboxamide (4f)

Yellow crystals (80%), crystallized from dioxane, mp. 240°C, IR (ν, cm^{-1}): 3438, 3402, 3253, 3153 (NH_2 and amidic NH_2), 1669 (amide CO); MS (m/z) = 303 (M^+, 100%, which corresponds to the molecular weight), 287 (M^+-NH_2, 33.1%), 286 (M^+-NH_2, −H, 21.8%), 285 (M^+-NH_2, −2H, 13.3%), 257 (M^+-CONH_2, −2H, 34.1%). Anal. for $C_{14}H_{10}ClN_3OS$ (303), calcd./found (%): C (55.35/55.32), H (3.32/3.29), Cl (11.67/11.69), N (13.83/13.85), and S (10.56/10.58).

(3-Amino-6-phenylthieno[2,3-b]pyridin-2-yl)(phenyl)methanone (17a)

Yellow crystals (80%), crystallized from ethanol, mp. 183°C, IR (ν, cm^{-1}): 3466, 3376 (NH_2), 3076 (C−H aromatic), 1678 (CO); MS (m/z) = 330 (M^+, 53.8%, which corresponds to the molecular weight), 329 (M^+-H, 29.7%), 314 (M^+-NH_2, 17.9%), 225 (M^+-COPh, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 5.99 (s, 2H, NH_2), 7.11–8.54 (m, 11H, Ar, and pyridinyl C_4H), and 9.68 (m, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{14}N_2OS$ (330), calcd./found (%): C (72.70/72.67), H (4.27/4.29), N (8.48/8.51), and S (9.71/9.74).

[3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridin-2-yl](phenyl)methanone (17b)

Yellow crystals (55%), crystallized from ethanol, mp. 195°C, IR (ν, cm^{-1}): 2987, 2867 (C−H stretching of aliphatic), 3458, 3373 (NH_2), 3066 (C−H aromatic), 1669 (CO); MS (m/z) = 344

(M^+, 58.2%, which corresponds to the molecular weight), 343 (M^+-H, 33.3%), 328 (M^+-NH_2, 32.7%), 238 (M^+-COPh, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 0.96 (s, 3H, CH_3), 5.98 (s, 2H, NH_2), 7.24–8.69 (m, 10H, Ar, and pyridinyl C_4H), and 9.583 (m, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{16}N_2OS$ (344), calcd./found (%): C (73.23/73.25), H (4.68/4.71), N (8.13/8.16), and S (9.31/9.34).

[3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridin-2-yl](phenyl)methanone (17c)

Yellow crystals (72%), crystallized from ethanol, mp. 213°C, IR (ν, cm^{-1}): 3463, 3377 (NH_2), 3068 (C−H aromatic), 1677 (CO); MS (m/z) = 364 (M^+, 55.9%, which corresponds to the molecular weight), 363 (M^+-H, 21.9%), 348 (M^+-NH_2, 33.2%), 258 (M^+-COPh, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 6.04 (s, 2H, NH_2), 7.11–8.58 (m, 10H, Ar, and pyridinyl C_4H), and 9.65 (m, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{13}ClN_2OS$ (364), calcd./found (%): C (65.84/65.87), H (3.59/3.61), Cl (9.72/9.69), N (7.68/7.66), and S (8.79/8.81).

(3-Amino-6-phenylthieno[2,3-b]pyridin-2-yl)(4-chlorophenyl)methanone (17d)

Yellow crystals (70%), crystallized from ethanol, mp. 206°C, IR (ν, cm^{-1}): 3422, 3319 (NH_2), 3072 (C−H aromatic), 1677 (CO); MS (m/z) = 364 (M^+, 55.2%, which corresponds to the molecular weight), 363 (M^+-H, 32.8%), 348 (M^+-NH_2, 23.7%), 225 ($M^+-COC_6H_4-$p-Cl, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 5.83 (s, 2H, NH_2), 7.11–8.62 (m, 10H, Ar, and pyridinyl C_4H), and 9.50 (m, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{13}ClN_2OS$ (364), calcd./found (%): C (65.84/65.87), H (3.59/3.61), Cl (9.72/9.69), N (7.68/7.66), and S (8.79/8.81).

[3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridin-2-yl](4-chlorophenyl)methanone (17e)

Yellow crystals (55%), crystallized from ethanol, mp. 166°C, IR (ν, cm^{-1}): 2973, 2889 (C−H stretching of aliphatic), 3412, 3338 (NH_2), 3056 (C−H aromatic), 1679 (CO); MS (m/z) = 378 (M^+, 64.3%, which corresponds to the molecular weight), 377 (M^+-H, 33.1%), 362 (M^+-NH_2, 9.7%), 239 ($M^+-COC_6H_4-$p-Cl, 100%);^1H NMR (DMSO-d_6) (δ, ppm): 1.11 (s, 3H, CH_3), 6.15 (s, 2H, NH_2), 7.14–8.86 (m, 9H, Ar, and pyridinyl C_4H), and 9.67 (m, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{15}ClN_2OS$ (378), calcd./found (%): C (66.57/66.59), H (3.99/4.02), Cl (9.36/9.33), N (7.39/7.41), and S (8.46/8.48).

[3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridin-2-yl](4-chlorophenyl)methanone (17f)

Yellow crystals (65%), crystallized from dioxane, mp. 237°C, IR (ν, cm^{-1}): 3422, 3344 (NH_2), 3076 (C−H aromatic), 1677 (CO); MS (m/z) = 399 (M^+, 44.8%, which corresponds to the molecular weight), 398 (M^+-H, 23.9%), 383 (M^+-NH_2, 27.3%), 260 ($M^+-COC_6H_4-$p-Cl, 100%);^1H NMR (DMSO-d_6) (δ, ppm): 6.17 (s, 2H, NH_2), 7.13–8.91 (m, 9H, Ar, and pyridinyl C_4H), and 9.58 (m, 1H, pyridinyl C_4H). Anal. for $C_{20}H_{12}Cl_2N_2OS$ (399), calcd./found (%): C (60.16/60.18), H (3.03/3.05), Cl (17.76/17.74), N (7.02/6.99), and S (8.03/8.00).

(3-Amino-6-phenylthieno[2,3-b]pyridin-2-yl)(4-methylphenyl)methanone (17g)

Yellow crystals (76%), crystallized from ethanol, mp. 226°C, IR (ν, cm^{-1}): 2965, 2884 (C−H stretching of aliphatic), 3437, 3322 (NH_2), 3066 (C−H aromatic), 1688 (CO); MS (m/z) = 344 (M^+, 63.4%, which corresponds to the molecular weight), 343 (M^+-H, 18.9%), 328 (M^+-NH_2, 44.7%), 278 (M^+-COPh, 100%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.11 (s, 3H, CH_3), 5.93 (s, 2H, NH_2), 7.12–8.68 (m, 10H, Ar, and pyridinyl C_4H), and 9.582 (m, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{16}N_2OS$ (344), calcd./found (%): C (73.23/73.25), H (4.68/4.71), N (8.13/8.16), and S (9.31/9.34).

[3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridin-2-yl](4-methylphenyl)methanone (17h)

Brown crystals (65%), crystallized from ethanol, mp. 215°C, IR (ν, cm^{-1}): 2958, 2877 (C−H stretching of aliphatic), 3421, 3317 (NH_2), 3082 (C−H aromatic), 1672 (CO); MS (m/z) = 358 (M^+, 55.7%, which corresponds to the molecular weight), 357 (M^+−H, 23.7%), 342 (M^+-NH_2, 31.9%), 278 ($M^+-COC_6H_4$−p-CH_3, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.20 (s, 6H, two CH_3), 5.96 (s, 2H, NH_2), 7.15–8.69 (m, 9H, Ar, and pyridinyl C_4H), and 9.63 (m, 1H, pyridinyl C_4H). Anal. for $C_{22}H_{18}N_2OS$ (358), calcd./found (%): C (73.71/73.69), H (5.06/5.09), N (7.82/7.85), and S (8.95/8.97).

[3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridin-2-yl](4-methylphenyl)methanone (17i)

Red crystals (69%), crystallized from ethanol, mp. 220°C, IR (ν, cm^{-1}): 2964, 2896 (C−H stretching of aliphatic), 3417, 3322 (NH_2), 3076 (C−H aromatic), 1669 (CO); MS (m/z) = 378 (M^+, 34.9%, which corresponds to the molecular weight), 377 (M^+−H, 18.6%), 362 (M^+-NH_2, 11.8%), 298 ($M^+-COC_6H_4$−p-CH_3, 100%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.15 (s, 3H, CH_3), 6.10 (s, 2H, NH_2), 7.14–8.73 (m, 9H, Ar, and pyridinyl C_4H), and 9.59 (m, 1H, pyridinyl C_4H). Anal. for $C_{21}H_{15}ClN_2OS$ (378), calcd./found (%): C (66.57/66.59), H (3.99/4.02), Cl (9.36/9.33), N (7.39/7.41), and S (8.46/8.48).

1-(3-Amino-6-phenylthieno[2,3-b]pyridin-2-yl)ethanone (20a)

Yellow crystals (68%), crystallized from ethanol, mp. 218°C, IR (ν, cm^{-1}): 2976, 2856 (C−H stretching of aliphatic), 3069 (C−*H*, aromatic), 2209 (CN), 1715 (CO); MS (m/z) = 268 (M^+, 100%, which corresponds to the molecular weight), 367 (M^+−H, 32.4%), 266 (M^+−2H, 17.3%), 225 (M^+-COCH_3, 22.8%), 211 ($M^+-CH_2COCH_3$, 53.7%), 179 ($M^+-SCH_2COCH_3$, 62.8%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.36 (s, 3H, $-COCH_3$), 4.28 (s, 2H, $-SCH_2-$), 7.11–8.59 (m, 6H, Ar, pyridinyl C_5H), 9.56 (s, 1H, pyridinyl C_4H). Anal. for $C_{15}H_{12}N_2OS$ (268), calcd./found (%): C (67.14/67.16), H (4.51/4.53), N (10.44/10.47), and S (11.95/11.98).

1-[3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridin-2-yl]ethanone (20b)

Yellow crystals (77%), crystallized from ethanol, mp. 228°C, IR (ν, cm^{-1}): 2959, 2877 (C−H stretching of aliphatic), 3077 (C−*H*, aromatic), 2215 (CN), 1711 (CO); MS (m/z) = 282 (M^+, 100%, which corresponds to the molecular weight), 267 (M^+-CH_3, 37.8%), 239 (M^+-CH_3CO, 52.1%), 225 ($M^+-CH_2COCH_3$, 44.3%), 193 ($M^+-SCH_2COCH_3$, 66.3%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.11 (s, 3H, CH_3), 2.56 (s, 3H, $-COCH_3$), 4.30 (s, 2H, $-SCH_2-$), 7.14–8.58 (m, 5H, Ar, pyridinyl C_5H), 9.53 (s, 1H, pyridinyl C_4H). Anal. for $C_{16}H_{14}N_2OS$ (282), calcd./found (%): C (68.06/68.03), H (5.00/4.97), N (9.92/9.89), and S (11.36/11.33).

1-[3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridin-2-yl]ethanone (20c)

Yellow crystals (66%), crystallized from ethanol, mp. 215°C, IR (ν, cm^{-1}): 2967, 2869 (C−H stretching of aliphatic), 3069 (C−*H*, aromatic), 2219 (CN), 1709 (CO); MS (m/z) = 302 (M^+, 100%, which corresponds to the molecular weight), 287 (M^+-CH_3, 19.6%), 259 (M^+-CH_3CO, 43.7%), 245 ($M^+-CH_2COCH_3$, 32.8%), 213 ($M^+-SCH_2COCH_3$, 56.8%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.42 (s, 3H, $-COCH_3$), 4.22 (s, 2H, $-SCH_2-$), 7.10–8.55 (m, 5H, Ar, pyridinyl C_5H),

9.58 (s, 1H, pyridinyl C_4H). Anal. for $C_{15}H_{11}ClN_2OS$ (302), calcd./found (%): C (59.50/59.53), H (3.66/3.68), Cl (11.71/11.74), N (9.25/9.28), and S (10.59/10.56).

3-Amino-6-phenylthieno[2,3-b]pyridine-2-carboxylic acid (24a)

Brown crystals (55%), crystallized from ethanol, mp. 199°C, IR (ν, cm^{-1}): 3084 (C−H aromatic), 3473 (NH_2), 3275–3472 (acidic OH); MS (m/z): 270 (M^+, 100%, which corresponds to the molecular weight), 253 (M^+-OH, 53.2%), 225 (M^+-COOH, 28.9%); ^1H NMR (DMSO-d_6) (δ, ppm): 5.35 (s, 2H, NH_2), 7.13–8.25 (m, 6H, Ar, pyridinyl C_5H), 9.54 (s, 1H, pyridinyl C_4H), and 14.52 (s, br., 1H, COO*H*). Anal. for $C_{14}H_{10}N_2O_2S$ (270), calcd./found (%): C (62.21/62.18), H (3.73/3.71), N (10.36/10.39), and S (11.86/11.84).

3-Amino-6-(4-methylphenyl)thieno[2,3-b]pyridine-2-carboxylic acid (24b)

Brown crystals (75%), crystallized from ethanol, mp. 212°C, IR (ν, cm^{-1}): 2985, 2879 (C−H stretching of aliphatic), 3088 (C−H aromatic), 3477 (NH_2), 3235–3479 (acidic OH); MS (m/z): 284 (M^+, 100%, which corresponds to the molecular weight), 267 (M^+-OH, 53.2%), 239 (M^+-COOH, 33.7%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.13 (s, 3H, CH_3), 5.32 (s, 2H, NH_2), 7.16–8.58 (m, 5H, Ar, pyridinyl C_5H), 9.59 (s, 1H, pyridinyl C_4H), and 14.12 (s, br., 1H, *COO*H). Anal. for $C_{15}H_{12}N_2O_2S$ (284), calcd./found (%): C (63.36/63.38), H (4.25/4.28), N (9.85/9.82), and S (11.28/11.31).

3-Amino-6-(4-chlorophenyl)thieno[2,3-b]pyridine-2-carboxylic acid (24c)

Yellow crystals (69%), crystallized from ethanol, mp. 200°C, IR (ν, cm^{-1}): 3076 (C−H aromatic), 3474 (NH_2), 3235–3479 (acidic OH); MS (m/z): 304 (M^+, 100%, which corresponds to the molecular weight), 287 (M^+-OH, 43.8%), 259 (M^+-COOH, 13.3%); ^1H NMR (DMSO-d_6) (δ, ppm): 5.53 (s, 2H, NH_2), 7.13–8.55 (m, 5H, Ar, pyridinyl C_5H), 9.38 (s, 1H, pyridinyl C_4H), and 14.33 (s, br., 1H, COO*H*). Anal. for $C_{14}H_9ClN_2O_2S$ (304), calcd./found (%): C (55.18/55.16), H (2.98/3.01), Cl (11.63/11.65), N (9.19/9.22), and S (10.52/10.55).

Synthesis of 6a–6c (general method)

A solution of each of **4a**–**4f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol) and formic acid (20 ml) was heated under reflux for 6 h. The excess solvent was evaporated. The solids that were formed were collected by filtration, dried, and crystallized from dioxane to give **6a**–**6c**, respectively.

7-Phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6a)

White crystals (80%), crystallized from ethanol, mp. 183°C, IR (ν, cm^{-1}): 3173 (NH), 3088 (C−H aromatic), 1676 (CO); MS (m/z): 279 (M^+, 86.3%, which corresponds to the molecular weight), 278 (M^+-H, 100%), 277 (M^+-2H, 22.7%), 252 (M^+-NCH, 8.7%), 251 (M^+-CO, 21.3%), 223 ($M^+-CONHCH$, 32.7%). Anal. for $C_{15}H_9N_3OS$ (279), calcd./found (%): C (64.50/64.53), H (3.25/3.23), N (15.04/15.06), and S (11.48/11.50).

7-(4-Methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6b)

White crystals (78%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 2967, 2873 (C−H stretching of aliphatic), 3168 (NH), 3075 (C−H aromatic), 1670 (CO); MS (m/z): 293 (M^+,

55.7%, which corresponds to the molecular weight), 292 (M^+-H, 100%), 291 (M^+-2H, 17.9%), 266 (M^+-NCH, 22.3%), 265 (M^+-CO, 9.9%), 237 ($M^+-CONHCH$, 19.1%). Anal. for $C_{16}H_{11}N_3OS$ (293), calcd./found (%): C (65.51/65.53), H (3.78/3.81), N (14.32/14.29), and S (10.93/10.90).

7-(4-Chlorophenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6c)

Yellow crystals (70%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 3166 (NH), 3053 (C−H aromatic), 1669 (CO); MS (m/z): 313 (M^+, 69.1%, which corresponds to the molecular weight), 312 (M^+-H, 100%), 313 (M^+-2H, 19.3%), 286 (M^+-NCH, 15.1%), 285 (M^+-CO, 33.8%), 257 ($M^+-CONHCH$, 17.1%). Anal. for $C_{15}H_8ClN_3OS$ (313), calcd./found (%): C (57.42/57.45), H (2.57/2.60), Cl (11.30/11.33), N (13.39/13.37), and S (10.22/10.25).

Synthesis of 8a–8c (general method)

A solution of each of **4a**–**4f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol) in acetic anhydride (20 ml) was heated under reflux for 6 h; the excess solvents were evaporated. The solids that were so formed were collected by filtration and crystallized from dioxane to give **8a**–**8c**, respectively.

2-Methyl-7-phenylpyrido[3′,2′:4, 5]thieno[3,2-d]pyrimidin-4(3H)-one (8a)

Green crystals (67%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 2982, 2872 (C−H stretching of aliphatic), 3138 (NH), 3064 (C−H aromatic), 1669 (CO); MS (m/z): 293 (M^+, 100%, which corresponds to the molecular weight), 292 (M^+-H, 44.9%), 278 (M^+-CH_3, 31.8%), 251 ($M^+-NHCCH_3$, 33.7%), 223 ($M^+-CONHCCH_3$, 37.1%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.25 (s, 3H, CH_3); 7.10–8.65 (m, 6H, Ar, pyridinyl C_9H), 9.24 (s, 1H, pyridinyl C_8H); 12.63 (s, 1H, NH). Anal. for $C_{16}H_{11}N_3OS$ (293), calcd./found (%): C (65.51/65.53), H (3.78/3.81), N (14.32/14.29), and S (10.93/10.90).

2-Methyl-7-(4-methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (8b)

Yellow crystals (57%), crystallized from DMF, mp. >300°C, IR (ν, cm^{-1}): 2988, 2879 (C−H stretching of aliphatic), 3155 (NH), 3077 (C−H aromatic), 1673 (CO); MS (m/z): 307 (M^+, 100%, which corresponds to the molecular weight), 306 (M^+-H, 32.5%), 292 (M^+-CH_3, 45.1%), 265 ($M^+-NHCCH_3$, 22.3%), 237 ($M^+-CONHCCH_3$, 19.1%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 0.89 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); 7.04–8.73 (m, 5H, Ar, pyridinyl C_9H), 9.51 (s, 1H, pyridinyl C_8H); 12.55 (s, 1H, NH). Anal. for $C_{17}H_{13}N_3OS$ (307), calcd./found (%): C (66.43/66.45), H (4.26/4.29), N (13.67/13.69), and S (10.43/10.45).

7-(4-Chlorophenyl)-2-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (8c)

Yellow crystals (63%), crystallized from dioxane, mp. 295°C, IR (ν, cm^{-1}): 2981, 2893 (C−H stretching of aliphatic), 3165 (NH), 3078 (C−H aromatic), 1671 (CO); MS (m/z): 327 (M^+, 100%, which corresponds to the molecular weight), 326 (M^+-H, 22.3%), 312 (M^+-CH_3, 33.7%), 285 ($M^+-NHCCH_3$, 16.8%), 257 ($M^+-CONHCCH_3$, 22.7%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.52 (s, 3H, CH_3); 7.09–8.75 (m, 5H, Ar, pyridinyl C_9H), 9.62 (s, 1H, pyridinyl C_8H); 12.49 (s, 1H, NH). Anal. for $C_{16}H_{10}ClN_3OS$ (327), calcd./found (%): C (58.63/58.65), H (3.07/3.10), Cl (10.82/10.85), N (12.82/12.79), and S (9.78/9.81).

Synthesis of 10a−10c (general method)

Sodium nitrite solution (2.0 g in 10 ml water) was added to a solution of compounds **4a**–**4f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (10 ml) at 0°C and stirred for 5 min. The mixture was allowed to stand at room temperature for 30 min. The solids that precipitated on dilution with water were collected and crystallized from dioxane to give **10a**–**10c**, respectively.

7-Phenylpyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (10a)

Yellow crystals (86%), crystallized from dioxane, mp. 233°C, IR (ν, cm^{-1}): 3423 (NH), 3073 (C−H aromatic), 1666 (CO); MS (m/z): 280 (M^+, 100%, which corresponds to the molecular weight), 279 (M^+-H, 85.4%), 278 (M^+-2H, 58.7%), 251 (M^+-NHN, 33.7%). Anal. for $C_{14}H_8N_4OS$ (280), calcd./found (%): C (59.99/60.01), H (2.88/2.85), N (19.99/20.02), and S (11.44/11.47).

7-(4-Methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (10b)

Yellow crystals (85%), crystallized from dioxane, mp. 238°C, IR (ν, cm^{-1}): 3452 (NH), 3085 (C−H aromatic), 1677 (CO); MS (m/z): 294 (M^+, 100%, which corresponds to the molecular weight), 293 (M^+-H, 79.6%), 292 (M^+-2H, 55.3%), 265 (M^+-NHN, 17.5%). Anal. for $C_{15}H_{10}N_4OS$ (294), calcd./found (%): C (61.21/61.19), H (3.42/3.45), N (19.04/19.06), and S (10.89/10.92).

7-(4-Chlorophenyl)pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (10c)

Yellow crystals (83%), crystallized from ethanol, mp. 202°C, IR (ν, cm^{-1}): 3445 (NH), 3068 (C−H aromatic), 1673 (CO); MS (m/z): 314 (M^+, 100%, which corresponds to the molecular weight), 313 (M^+-H, 76.4%), 312 (M^+-2H, 52.3%), 285 (M^+-NHN, 31.1%). Anal. for $C_{14}H_7ClN_4OS$ (314), calcd./found (%): C (53.42/53.45), H (2.24/2.27), Cl (11.26/11.23), N (17.80/17.77), and S (10.19/10.21).

Synthesis of* 12*a*−12*c* *(general method)

A solution of each of **4a**–**4f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol) and phenyl isothiocyanate (0.40 g, 3 mmol) in pyridine (20 ml) was heated under reflux for 48 h. The reaction mixture was then cooled, poured into ice-cold water, and neutralized with a few drops of acetic acid and the solid was collected by filtration and crystallized from dioxane to give **12a**–**12c**, respectively.

4-Imino-3,7-diphenyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyramidine-2(1H)-thione (12a)

Yellow crystals (73%), crystallized from dioxane, mp. 284°C, IR (ν, cm^{-1}): 3358, 3222 (2NH), 3067 (C−H aromatic), 1555 (C=S); MS (m/z): 386 (M^+, 100%, which corresponds to the molecular weight), 385 (M^+-H, 58.7%), 384 (M^+-2H, 46.9%), 309 ($M^+-C_6H_5$, 37.3%), 306 (M^+-2H, C_6H_5, 44.1%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 5.55 (s, 1H, NH at 1-position); 7.24–8.97 (m, 11H, Ar, pyridinyl C_9H), 9.54 (s, 1H, pyridinyl C_8H); 13.23 (s, 1H, NH at 4-position).

Anal. for $C_{21}H_{14}N_4S_2$ (386), calcd./found (%): C (65.26/65.29), H (3.65/3.62), N (14.50/14.53), and S (16.59/16.61).

4-Imino-7-(4-methylphenyl)-3-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine -2(1H)-thione (12b)

Yellow crystals (91%), crystallized from DMF, mp. >300°C, IR (ν, cm^{-1}): 2988, 2874 (C−H stretching of aliphatic), 3355, 3216 (2NH), 3076 (C−H aromatic), 1547 (C=S); MS (m/z): 400 (M^+, 100%, which corresponds to the molecular weight), 399 (M^+-H, 36.9%), 398 (M^+-2H, 44.1%), 323 ($M^+-C_6H_5$, 24.1%), 321 (M^+-2H, C_6H_5, 31.7%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.02 (s, 3H, CH_3), 5.27 (s, 1H, NH at 1-position); 7.17–8.96 (m, 10H, Ar, pyridinyl C_9H), 9.70 (s, 1H, pyridinyl C_8H); 13.54 (s, 1H, NH at 4-position). Anal. for $C_{22}H_{16}N_4S_2$ (400), calcd./found (%): C (65.97/66.00), H (4.03/4.05), N (13.99/14.01), and S (16.01/15.98).

7-(4-Chlorophenyl)-4-imino-3-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine -2(1H)-thione (12c)

Yellow crystals (78%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 3357, 3214 (2NH), 3072 (C−H aromatic), 1558 (C=S); MS (m/z): 420 (M^+, 100%, which corresponds to the molecular weight), 419 (M^+-H, 48.3%), 418 (M^+-2H, 38.3%), 343 ($M^+-C_6H_5$, 55.8%), 341 (M^+-2H, C_6H_5, 31.8%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 5.27 (s, 1H, NH at 1-position); 7.18–8.910 (m, 10H, Ar, pyridinyl C_9H), 9.69 (s, 1H, pyridinyl C_8H); 13.45 (s, 1H, NH at 4-position). Anal. for $C_{21}H_{13}ClN_4S_2$ (420), calcd./found (%): C (59.92/59.89), H (3.11/3.14), Cl (8.42/8.45), N (13.31/13.33), and S (15.24/15.26).

Synthesis of 14a−14c (general method)

A solution of each of **4a**–**4f** (0.80, 0.84, 0.90, 0.75, 0.79, and 0.85 g, 3 mmol) and carbon disulfide (5 ml) in pyridine (20 ml) was heated under reflux for 48 h. The reaction mixture was then cooled, poured into ice-cold water, and neutralized with a few drops of acetic acids; the solids that were so formed were collected by filtration, dried, and crystallized from ethanol to give **14a**–**14c**, respectively.

7-Phenyl-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (14a)

Yellow crystals (79%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 3344 (NH), 3069 (C−H aromatic), 1552 (C=S); MS (m/z): 311 (M^+, 100%, which corresponds to the molecular weight), 310 (M^+-H, 55.3%), 297 (M^+-N, 33.9%), 295 (M^+-H, NH, 30.8%), 279 (M^+-S, 14.8%), 253 (M^+-CSN, 22.3%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.10–8.73 (m, 6H, Ar, pyridinyl C_9H), 9.52 (s, 1H, pyridinyl C_8H), 12.55 (s, 1H, NH at 3-position); 13.78 (s, 1H, NH at 3-position). Anal. for $C_{15}H_9N_3OS_2$ (311), calcd./found (%): C (57.86/57.89), H (2.91/2.88), N (13.49/13.51), and S (20.60/20.62).

7-(4-Methylphenyl)-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (14b)

Yellow crystals (90%), crystallized from dioxane, mp. 296°C, IR (ν, cm^{-1}): 2978, 2876 (C−H stretching of aliphatic), 3338 (NH), 3077 (C−H aromatic), 1555 (C=S); MS (m/z): 325 (M^+, 100%, which corresponds to the molecular weight), 324 (M^+-H, 34.8%), 311 (M^+-N, 26.3%),

309 (M^+-H, NH, 22.1%), 293 (M^+-S, 32.1%), 267 (M^+-CSN, 12.9%); ^1H NMR (DMSO-d_6) (δ, ppm): 1.21 (s, 3H, CH_3), 7.21–8.82 (m, 5H, Ar, pyridinyl C_9H), 9.62 (s, 1H, pyridinyl C_8H), 12.44 (s, 1H, NH at 3-position); 13.20 (s, 1H, NH at 3-position). Anal. for $C_{16}H_{11}N_3OS_2$ (325), calcd./found (%): C (59.06/59.09), H (3.41/3.39), N (12.91/12.88), and S (19.71/19.68).

7-(4-Chlorophenyl)-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (14c)

Yellow crystals (83%), crystallized from DMF, mp. >300°C, IR (ν, cm^{-1}): 3348 (NH), 3088 (C−H aromatic), 1550 (C=S); MS (m/z): 345 (M^+, 100%, which corresponds to the molecular weight), 344 (M^+-H, 32.8%), 331 (M^+-N, 48.2%), 329 (M^+-H, NH, 21.7%), 313 (M^+-S, 24.7%), 287 (M^+-CSN, 17.9%); ^1H NMR (DMSO-d_6) (δ, ppm): 7.18–8.35 (m, 5H, Ar, pyridinyl C_9H), 9.64 (s, 1H, pyridinyl C_8H), 12.63 (s, 1H, NH at 3-position); 13.55 (s, 1H, NH at 3-position). Anal. for $C_{15}H_8ClN_3OS_2$ (345), calcd./found (%): C (52.10/52.13), H (2.33/2.36), Cl (10.25/10.28), N (12.15/12.13), and S (18.54/18.57).

Synthesis of 25a−25c (general method)

A solution of each of **24a**–**24c** (0.81, 0.84, and 0.90 g, 1 mmol) and acetic anhydride (20 ml) was heated under reflux for 4 h. The excess solvent was evaporated and then cooled. The solids that were so formed were collected by filtration and crystallized from dioxane to give **25a**–**25c**, respectively.

2-Methyl-7-phenyl-4H-pyrido[3′,2′:4,5]thieno[3,2-d][1,3]oxazin-4-one (25a)

Gray crystals (67%), crystallized from dioxane, mp. 278°C, IR (ν, cm^{-1}): 2987, 2873 (C−H stretching of aliphatic), 3077 (C−H aromatic), 1731 (CO); MS (m/z): 294 (M^+, 100%, which corresponds to the molecular weight), 279 (M^+-CH_3, 33.12%), 253 (M^+-NCCH_3, 23.7%), 251 (M^+-2H, $NCCH_3$, 15.7%), 250 (M^+-CO_2, 38.9%); ^1H NMR (DMSO-d_6) (δ, ppm): 2.36 (s, 3H, CH_3); 7.11–8.51 (m, 6H, Ar, pyridinyl C_9H), 9.52 (s, 1H, pyridinyl C_8H). Anal. for $C_{16}H_{10}N_2O_2S$ (294), calcd./found (%): C (65.29/65.31), H (3.42/3.45), N (9.52/9.49), and S (10.89/10.87).

2-Methyl-7-(4-methylphenyl)-4H-pyrido[3′,2′:4,5]thieno[3,2-d][1,3]oxazin-4-one (25b)

Brown crystals (66%), crystallized from DMF, mp. > 300°C, IR (ν, cm^{-1}): 2984, 2879 (C−H stretching of aliphatic), 3072 (C−H aromatic), 1727 (CO); MS (m/z): 308 (M^+, 100%, which corresponds to the molecular weight), 293 (M^+-CH_3, 22.59%), 267 (M^+-NCCH_3, 53.2%), 265 (M^+-2H, $NCCH_3$, 9.18%), 264 (M^+-CO_2, 75.3%); ^1H NMR (DMSO-d_6) (δ, ppm): 0.98 (s, 3H, CH_3), 2.53 (s, 3H, CH_3); 7.13–8.58 (m, 5H, Ar, pyridinyl C_9H), 9.58 (s, 1H, pyridinyl C_8H). Anal. for $C_{17}H_{12}N_2O_2S$ (308), calcd./found (%): C (66.22/66.24), H (3.92/3.95), N (9.08/9.11), and S (10.40/10.43).

7-(4-Chlorophenyl)-2-methyl-4H-pyrido[3′,2′:4,5]thieno[3,2-d][1,3]oxazin-4-one (25c)

Brown crystals (65%), crystallized from DMF, mp. >300°C, IR (ν, cm^{-1}): 2975, 2868 (C−H stretching of aliphatic), 3063 (C−H aromatic), 1729 (CO); MS (m/z): 328 (M^+, 100%, which corresponds to the molecular weight), 313 (M^+-CH_3, 17.33%), 287 (M^+-NCCH_3, 33.9%), 285 (M^+-2H, $NCCH_3$, 14.22%), 284 (M^+-CO_2, 62.8%); ^1H NMR (DMSO-d_6) (δ, ppm): 2.56 (s, 3H, CH_3); 7.10–8.54 (m, 5H, Ar, pyridinyl C_9H), 9.53 (s, 1H, pyridinyl C_8H). Anal. for

$C_{16}H_9ClN_2O_2S$ (328), calcd./found (%): C (58.45/58.48), H (2.76/2.79), Cl (10.78/10.76), N (8.52/8.55), and S (9.75/9.73).

Synthesis of 27a−27f (general method)

A solution of each of **26a**–**26c** (0.88, 0.92, and 0.98 g, 3 mmol) and aniline or p-toluidine (0.27 and 0.36g, 3 mmol) in acetic acid (20 ml) was heated under reflux for 3 h. The excess solvent was evaporated and then cooled. The solids that were so formed were collected by filtration, dried, and crystallized from acetic acid to give **28a**–**28f**, respectively.

2-Methyl-3,7-diphenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (27a)

Yellow crystals (77%), crystallized from dioxane, mp. 285°C, IR (ν, cm^{-1}): 2976, 2865 (C−H stretching of aliphatic), 3045 (C−H aromatic), 1676 (CO); MS (m/z); 369 (M^+, 100%, which corresponds to the molecular weight), 368 (M^+-H, 42.9%), 354 (M^+-CH_3, 33.5%), 341 (M^+-CO, 26.12%), 250 ($M^+-CONC_6H_5$, 17.22%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.53 (s, 3H, CH_3); 7.22–8.55 (m, 11H, Ar, pyridinyl C_9H), 9.56 (s, 1H, pyridinyl C_8H). Anal. for $C_{22}H_{15}N_3OS$ (369), calcd./found (%): C (71.52/71.55), H (4.09/4.12), N (11.37/11.39), and S (8.68/8.65).

2-Methyl-3-(4-methylphenyl)-7-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (27b)

Yellow crystals (65%), crystallized from dioxane, mp. 244°C, IR (ν, cm^{-1}): 2956, 2887 (C−H stretching of aliphatic), 3086 (C−H aromatic), 1678 (CO); MS (m/z); 383 (M^+, 100%, which corresponds to the molecular weight), 382 (M^+-H, 22.3%), 368 (M^+-CH_3, 33.5%), 355 (M^+-CO, 16.33%), 250 ($M^+-CONC_6H_4-p\text{-}CH_3$, 33.32%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 0.98 (s, 3H, CH_3), 2.56 (s, 3H, CH_3); 7.26–8.57 (m, 10H, Ar, pyridinyl C_9H), 9.58 (s, 1H, pyridinyl C_8H). Anal. for $C_{23}H_{17}N_3OS$ (383), calcd./found (%): C (72.04/72.06), H (4.47/4.50), N (10.96/10.98), and S (8.36/8.33).

2-Methyl-7-(4-methylphenyl)-3-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (27c)

Yellow crystals (58%), crystallized from ethanol, mp. 228°C, IR (ν, cm^{-1}): 2953, 2896 (C−H stretching of aliphatic), 3065 (C−H aromatic), 1672 (CO); MS (m/z); 383 (M^+, 100%, which corresponds to the molecular weight), 382 (M^+-H, 22.4%), 368 (M^+-CH_3, 63.1%), 355 (M^+-CO, 42.33%), 264 ($M^+-CONC_6H_5$, 27.34%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.55 (s, 6H, two CH_3); 7.23–8.54 (m, 10H, Ar, pyridinyl C_9H), 9.55 (s, 1H, pyridinyl C_8H). Anal. for $C_{23}H_{17}N_3OS$ (383), calcd./found (%): C (72.04/72.06), H (4.47/4.50), N (10.96/10.98), and S (8.36/8.33).

2-Methyl-3,7-bis(4-methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (27d)

Yellow crystals (54%), crystallized from dioxane, mp. 266°C, IR (ν, cm^{-1}): 2966, 2897 (C−H stretching of aliphatic), 3077 (C−H aromatic), 1669 (CO); MS (m/z); 397 (M^+, 100%, which corresponds to the molecular weight), 396 (M^+-H, 9.18%), 382 (M^+-CH_3, 13.7%), 369 (M^+-CO, 42.03%), 264 ($M^+-CONC_6H_4-p\text{-}CH_3$, 30.31%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 0.98 (s, 6H, two CH_3), 2.62 (s, 3H, CH_3); 7.20–8.36 (m, 9H, Ar, pyridinyl C_9H), 9.58 (s, 1H, pyridinyl C_8H).

Anal. for $C_{24}H_{19}N_3OS$ (397), calcd./found (%): C (72.52/72.49), H (4.82/4.85), N (10.57/10.60), and S (8.07/8.09).

7-(4-Chlorophenyl)-2-methyl-3-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (27e)

Brown crystals (77%), crystallized from dioxane, mp. 255°C, IR (ν, cm^{-1}): 3046 (C−H aromatic), 1672 (CO); MS (m/z); 403 (M^+, 100%, which corresponds to the molecular weight), 402 (M^+-H, 12.8%), 388 (M^+-CH_3, 42.2%), 275 (M^+-CO, 23.52%), 284 ($M^+-CONPh$, 27.19%); ^1H NMR (DMSO-d_6) (δ, ppm): 2.63 (s, 3H, CH_3); 7.16–8.47 (m, 10H, Ar, pyridinyl C_9H), 9.49 (s, 1H, pyridinyl C_8H). Anal. for $C_{22}H_{14}ClN_3OS$ (403), calcd./found (%): C (65.42/65.39), H (3.49/3.51), Cl (8.78/8.76), N (10.40/10.38), and S (7.94/7.92).

7-(4-Chlorophenyl)-2-methyl-3-(4-methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidin-4(3H)-one (27f)

Yellow crystals (77%), crystallized from ethanol, mp. 199°C, IR (ν, cm^{-1}): 2954, 2889 (C−H stretching of aliphatic), 3065 (C−H aromatic), 1674 (CO); MS (m/z); 417 (M^+, 100%, which corresponds to the molecular weight), 416 (M^+-H, 13.76%), 402 (M^+-CH_3, 32.6%), 389 (M^+-CO, 32.53%), 298 ($M^+-CONC_6H_4-p\text{-}CH_3$, 17.17%); ^1H NMR (DMSO-d_6) (δ, ppm): 0.98 (s, 3H, CH_3), 2.54 (s, 3H, CH_3); 7.14–8.55 (m, 9H, Ar, pyridinyl C_9H), 9.59 (s, 1H, pyridinyl C_8H). Anal. for $C_{23}H_{16}ClN_3OS$ (417), calcd./found (%): C (66.10/66.13), H (3.86/3.83), Cl (8.48/8.51), N (10.05/10.02), and S (7.67/7.64).

Synthesis of 29a–29c (general method)

A solution of each of **26a**–**26c** (0.88, 0.92, and 0.98 g, 3 mmol) in hydrazine hydrate (5 ml) and ethanol (20 ml) was heated under reflux for 2 h; the excess solvents were evaporated and then cooled. The solids that were so formed were collected by filtration, dried, and crystallized from acetic acid to give **29a**–**29c**, respectively.

3-Amino-2-methyl-7-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (28a)

Brown crystals (55%), crystallized from dioxane, mp. 244°C, IR (ν, cm^{-1}): 2987, 2867 (C−H stretching of aliphatic), 3455, 3228 (NH_2), 3054 (C−H aromatic), 1667 (CO); MS (m/z): 308 (M^+, 100%, which corresponds to the molecular weight), 307 (M^+-H, 34.28%), 293 (M^+-CH_3, 39.31%), 292 (M^+-NH_2, 54.22%), 279 (M^+-2H, CCH_3, 56.7%); ^1H NMR (DMSO-d_6) (δ, ppm): 2.56 (s, 3H, CH_3); 6.20 (br., 2H, NH_2); 7.13–8.53 (m, 6H, Ar, pyridinyl C_9H), 9.58 (s, 1H, pyridinyl C_9H). Anal. for $C_{16}H_{12}N_4OS$ (308), calcd./found (%): C (62.32/62.35), H (3.92/3.89), N (18.17/18.15), and S (10.40/10.38).

3-Amino-2-methyl-7-(4-methylphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (28b)

Yellow crystals (64%), crystallized from ethanol, mp. 195°C, IR (ν, cm^{-1}): 2977, 2898 (C−H stretching of aliphatic), 3439, 3233 (NH_2), 3060 (C−H aromatic), 1677 (CO); MS (m/z): 322 (M^+, 100%, which corresponds to the molecular weight), 321 (M^+-H, 13.58%), 317 (M^+-CH_3, 9.23%), 316 (M^+-NH_2, 55.34%), 293 (M^+-2H, CCH_3, 28.13%); ^1H NMR (DMSO-d_6) (δ, ppm): 0.89 (s, 3H, CH_3), 2.56 (s, 3H, CH_3); 6.24 (br., 2H, NH_2); 7.13–8.56 (m, 5H, Ar, pyridinyl C_9H),

9.54 (s, 1H, pyridinyl C_9H). Anal. for $C_{17}H_{14}N_4OS$ (322), calcd./found (%): C (63.33/63.31), H (4.38/4.35), N (17.38/17.40), and S (9.95/9.97).

3-Amino-7-(4-chlorophenyl)-2-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-(3H)-one (28c)

Brown crystals (66%), crystallized from dioxane, mp. 278°C, IR (ν, cm^{-1}): 2987, 2867 (C−H stretching of aliphatic), 3451, 3233 (NH_2), 3064 (C−H aromatic), 1669 (CO); MS (m/z): 342 (M^+, 100%, which corresponds to the molecular weight), 341 (M^+-H, 18.22%), 327 (M^+-CH_3, 19.72%), 326 (M^+-NH_2, 17.13%), 313 (M^+-2H, CCH_3, 36.3%); ^{1}H NMR (DMSO-d_6) (δ, ppm): 2.58 (s, 3H, CH_3); 6.24 (br., 2H, NH_2); 7.14–8.54 (m, 5H, Ar, pyridinyl C_9H), 9.59 (s, 1H, pyridinyl C_9H). Anal. for $C_{16}H_{11}ClN_4OS$ (342), calcd./found (%): C (56.06/56.03), H (3.23/3.21), Cl (10.34/10.37), N (16.34/16.32), and S (9.35/9.33).

Materials and methods

Detection of biological activity (sensitivity tests) using the Kirby-Bauer method

Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method (*27*). Briefly, 100 µl of the test bacteria/fungi was grown in 10 ml of fresh media until a count of approximately 10^8 cells/ml was reached for bacteria or of 10^5 cells/ml was reached for fungi (*28*); 100 µl of microbial suspension was spread onto agar plates corresponding to the broth in which the organisms were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from the primary agar plates and tested for susceptibility by the disc diffusion method; of the many media available, National Committee for Clinical Laboratory Standard (NCCLS) recommends Mueller-Hinton agar due to its good batch-to-batch reproducibility. For filamentous fungi, the disc diffusion method was performed by using the approved standard method (M38-A) for evaluating the susceptibilities of filamentous fungi to antifungal agents. For yeasts, the disc diffusion method was developed by using the approved standard method (M44-P). The plates were inoculated with filamentous fungi such as *Aspergillus flavus* at 25°C for 48 h; Gram (+) bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and Gram (-) bacteria such as *Escherichia coli* and *Pseudomonas aeurginosa* were incubated at 35–37°C for 24–48 h and yeasts such as *Candida albicans* were incubated at 30°C for 24–48 h and then the diameters of the inhibition zones were measured in millimeters (*27*). Standard discs of *Tetracycline* (antibacterial agent) and *Amphotericin B* (antifungal agent) served as positive controls for antimicrobial activity, but filter discs impregnated with 10 µl of a solvent (distilled water, chloroform, or DMSO) were used as a negative control. The agar that was used was the Mueller-Hinton agar that was rigorously tested for composition and pH. Furthermore, the depth of the agar in the plate is a factor to be considered in the disc diffusion method. This method is well documented and standard zones of inhibition have been determined for susceptible and resistant values. Blank paper disks (Schleicher & Schuell, Spain) with a diameter of 8.0 mm were impregnated with 10 µ of the tested concentration of the stock solution. When a filter paper disc impregnated with a tested chemical is placed on agar, the chemical diffuses from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc. If an organism is placed on the agar, it will not grow in the area around the disc if it is susceptible to the chemical. This area growth around the disc is known as the "zone of inhibition" or "clear zone". In the disc diffusion method, the zone diameters were measured with slipping calipers of the NCCLS. Agar-based methods such as the E-test and disk diffusion can be good alternatives because they are simpler and faster than the broth-based methods (*29*, *30*).

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