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SYNTHESIS, REACTIONS, AND ANTIMICROBIAL EVALUATION OF SOME POLYCONDENSED THIENOPYRIMIDINE DERIVATIVES

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Some novel indeno[2,1-b]thiophenes, indeno[1′,2′:4,5]thieno[2,3-d][1,2,3]triazines, indeno[1′,2′:4,5]thieno[2,3-d]pyrimidines, indeno[1′,2′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidines, and indeno[1′,2′:4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidines* 2–16 *were prepared starting with 2-aminoindeno[2,1-b]thiophene-3-carboxylic acid amide (1). Furthermore, the antimicrobial evaluation of the prepared products showed that many of them revealed promising antimicrobial activity.

Keywords: Antimicrobial evaluation; indeno[2,1-*b*]thiophenes; indenothienopyrimidines; thiazolothienopyrimidines; thienotriazolopyrimidines

INTRODUCTION

Fused thieno[2,3-*d*]pyrimidine derivatives are one of the most active classes of compounds because of their synthetic and effective biological importance.[1–3] They bear structural analogy and isoelectronic relation to purine and several substituted thieno[2,3-*d*]pyrimidine derivatives shown to exhibit prominent and versatile biological activities.[4,5] Recently, many of their derivatives have been synthesized as potential anticancer,[6] analgesic,[7] antimicrobial,[8] and antiviral agents.[9] Besides, prominent biological activities have been reported for [1,4]thiazolo[4,3-*a*]pyrimidine and [1,2,4]triazolopyrimidine derivivatives, such as antimicrobial,[10,11] analgesic,[12] and anti-inflammatory[13] activities. This work aimed to synthesize new compounds related to indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine derivatives and their fused [1,3]thiazolo[3,2-*a*]pyrimidine and [1,2,4]triazolo[4,3-*a*]pyrimidine derivatives, and to evaluate their antimicrobial activity.

RESULTS AND DISCUSSION

The starting material 2-aminoindeno[2,1-*b*]thiophene-3-carboxylic acid amide (**1**) was prepared[14] and then underwent cyclization with butyraldehyde or benzoyl chloride to afford thieno[2,3-*d*]pyrimidinone derivatives **2** and **3**, respectively.

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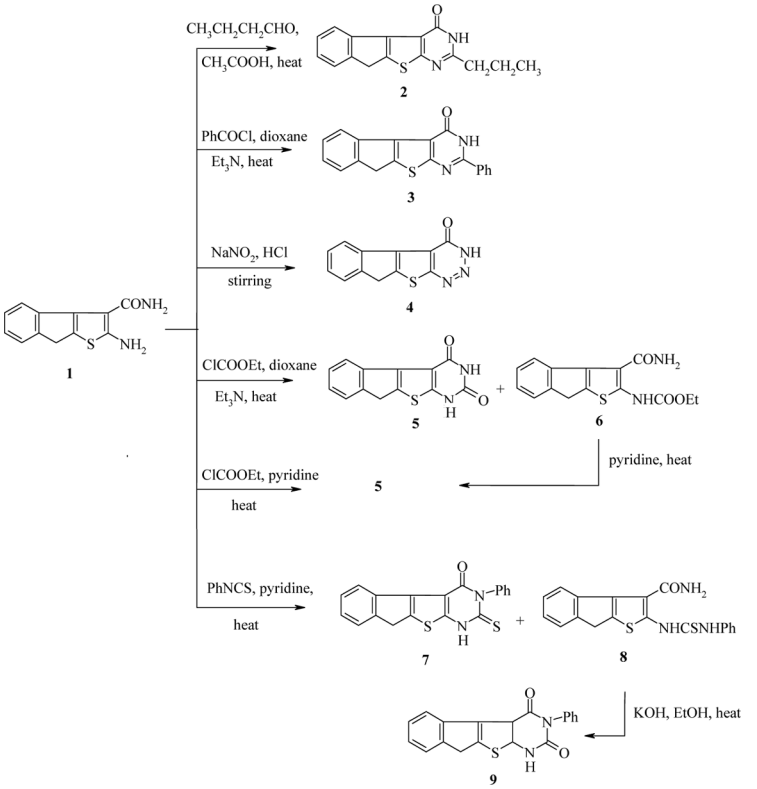
Analytical and spectral data of the aforementioned compounds are in agreement with the proposed structures (Experimental). In particular, the presence of propyl signals and phenyl signals in the ^{1}H NMR spectra of compounds **2** and **3** confirmed their structures.

Some reports[15,16] stated that the reaction of compounds analogous to compound **1** with nitrous acid gave the diazonium chloride derivative, which on boiling in alcohols gave unexpected carboxylic acid alkyl esters. Meanwhile, our attempts to cyclize compound **1** by stirring with nitrous acid gave the corresponding triazinone derivative **4** (Scheme 1). The structure of compound **4** was confirmed with spectral data, where its infrared (IR) spectrum showed bands at (ν, cm^{-1}): 3201 (NH) and 1678 (C=O) and its ^{1}H NMR spectrum showed a signal at δ 8.14 ppm for NH. Also, mass spectrometry (MS) gave the molecular ion peak at m/z 241 (M^+, 74%) (Experimental). Moreover, treatment of compound **1** with ethyl chloroformate in dry dioxane under reflux afforded not only the cyclized thieno[2,3-*d*]pyrimidindione derivative **5** but also a product assigned to the structure of compound **6**. Refluxing compound **6** in dry pyridine or compound **1** with ethyl chloroformate in dry pyridine gave in both cases the same product, which was assigned to the structure of compound **5** (Scheme 1, Experimental). The pyrimidindione derivative **5** could be formed



Scheme 1. Synthesis route of compounds **2–9**.

via the formation of derivative **6**, which was isolated and suffered cyclization to thieno[2,3-*d*]pyrimidindione derivative **5** under the conditions of the reaction (Scheme 1). Inspection of the IR spectrum of product **5** revealed the presence of 2 NH and 2 C=O signals, and MS gave the molecular ion peak at m/z 256 (M^+, 100%). Moreover, the ^{1}H NMR spectrum of product **6** showed signals at δ 1.05 and 4.05 ppm for CH_3 and CH_2, respectively (Experimental).

However, heating of compound **1** with phenyl isothiocyanate in dry pyridine gave a mixture of the thiourea derivative **8** in addition to the corresponding thioxo derivative **7**. Analytical and spectral data of the aforementioned compounds are in agreement with the proposed structures (see Experimental). Alkaline treatment of compound **8** with potassium hydroxide did not afford a product assigned to the structure of compound **7** but instead afforded the cyclized 3-phenyl thieno[2,3-*d*]pyrimidindione derivative **9**. Inspection of the IR spectrum of product **9** revealed the presence of NH and 2 C=O signals, and MS gave the molecular ion peak at m/z 332 (M^+, 100%). Moreover, the ^{1}H NMR spectrum of product **9** showed signals of NH and phenyl groups at δ 8.36 and 6.80–7.32 ppm, respectively (Experimental). The formation of the unexpected 3-phenyl thieno[2,3-*d*]pyrimidindione derivative **9** was obtained via formation of the thioxo derivative **7** at first, which on further boiling gave the corresponding pyrimidindione derivative **9**.[17]

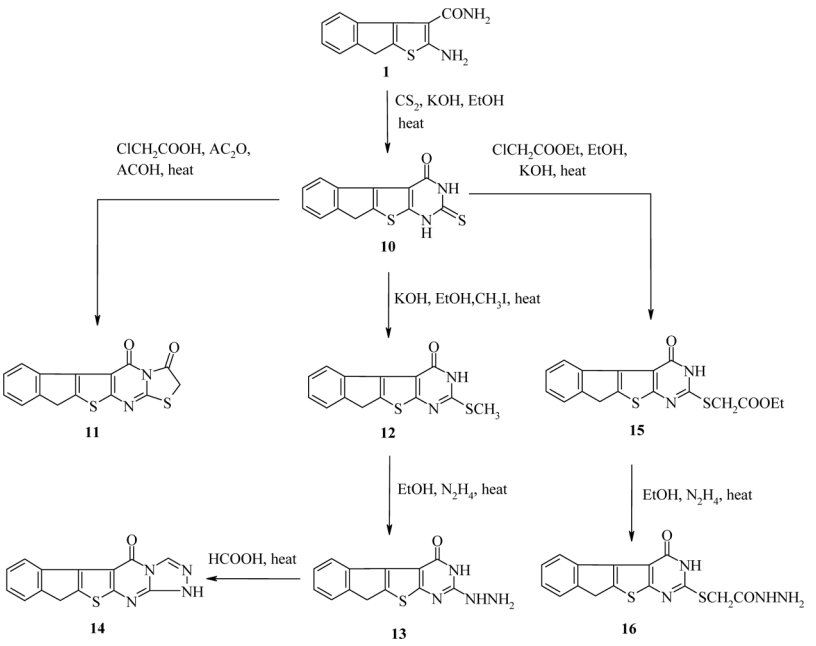
When compound **1** was heated under reflux temperature with carbon disulphide, it gave the corresponding 2-thioxo derivative **10**. Its IR spectrum revealed the presence of NH and C=O signals, and ^{1}H NMR spectrum gave signals at 3.20–3.40 and 12.52 ppm that were exchangeable with D_2O for SH and NH, respectively. Meanwhile, when compound **10** was refluxed with chloroacetic acid in a mixture of acetic acid–acetic anhydride (3:1), it afforded the corresponding thiazolothienopyrimidine derivative **11** (Scheme 2). The IR spectrum of compound **11** revealed the absence of the NH, as well as the presence of 2 C=O signals (Experimental). Also, ^{13}C NMR spectrum showed the presence of the methylene group in addition to the 2 C=O groups.

Methylation of compound **10** with methyl iodide in alcoholic potassium hydroxide solution afforded the corresponding 2-methylthio derivative **12**. The ^{1}H NMR spectrum of compound **12** showed the presence of methyl group at δ 2.40 ppm in addition to the peak corresponding to the NH group at δ 7.51 ppm. Its ^{13}C NMR spectrum showed the presence of the methyl group in addition to the absence of the peak corresponding to C=S.

Hydrazinolysis of compound **12**, in ethanol, gave 2-hydrazino-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (**13**) (Scheme 2). The ^{1}H NMR spectrum of compound **13** gave signals for NH, NH_2, exchangeable with D_2O, and its MS gave the molecular ion peak at $m/z = 270$ (M^+, 84%).

Furthermore, the structure of compound **13** was confirmed chemically by treatment with formic acid to afford the corresponding thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]-pyrimidine **14**. The IR and ^{1}H NMR spectra of compound **14** showed signals for NH, and its MS gave the molecular ion peak as a base peak at $m/z = 280$ (Experimental).

However, heating of compound **10** with ethyl chloroacetate in alcoholic potassium hydroxide solution gave a product assigned to the structure of compound **15**. The ^{1}H NMR and^{13}C NMR spectra of the latter compound revealed two methylene signals in addition to methyl signals (Experimental).



Scheme 2. Synthesis route of compounds **10–16**.

Moreover, hydrazinolysis of compound **15**, in ethanol, gave the acid hydrazide **16** (Scheme 2). Inspection of the IR and ^{1}H NMR spectra of product **16** revealed the presence of NH and NH_2 signals, and its MS gave the molecular ion peak at m/z 344 (M^+, 65%) (Experimental).

Antimicrobial Activity

The in vitro antimicrobial activity of the synthesized compounds was investigated against several pathogenic Gram-positive bacteria (*Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*), fungi (*Aspergillus niger*), and yeast (*Candida albicans*). All microorganisms were obtained from the culture collection of the Department of Natural and Microbial Products, National Research Centre, Dokki, Cairo, Egypt.

Method[18]

The cap-assay procedure using (g/L) peptone (6), yeast extract (3), meat extract (1.5), glucose (1), and agar (20) was used. The medium was sterilized and divided while hot (50–60 °C) in 15-mL portions among sterile Petri dishes 9 cm in diameter. One mL of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petri dish. Each of the tested compounds (0.5 g) was dissolved in 5 mL of dimethylformamide. An amount of 0.1 mL of test solution was placed on Whatman paper discs 9 mm in diameter, and the solvent was left to evaporate. These saturated discs were placed carefully on the surface

of the inoculated solid medium; each Petri dish contains at least three discs. The Petri dishes were incubated at 5 °C for 1 h to permit good diffusion, transferred to an incubator at 85 °C overnight, and then examined. The results were recorded by measuring the inhibition zone diameters. Dimethylsulfoxide (DMSO) as a solvent showed no inhibition zones. The results were compared to streptomycin and fusidic acid as reference drugs.

Results

As shown in Table 1, the antimicrobial activity of the tested compounds was evaluated by measuring the zone diameters, and the results were compared with those of well-known drugs (standards). In general, the tested compounds showed promising antimicrobial activity against bacteria more than fungi or yeast. Among the tested compounds, the substituted thiophene derivatives **1**, **6**, and **8** had the most significant antimicrobial activities. However, fusing a pyrimidine ring to the thiophene derivatives to form thieno[2,3-*d*]pyrimidine derivative as in compounds **2**, **3**, **5**, **7**, **9**, **10**, **12**, **13**, **15**, and **16** or a triazine ring to form a thieno[2,3-*d*][1,2,3]triazine derivative as in compound **4** decreased the antimicrobial activity. However, increased antimicrobial activity was achieved by fusing a thiazole or a triazole ring to thieno[2,3-*d*]pyrimidine ring system in compounds **11** and **14**, respectively.

Table 1. Antimicrobial activity of the prepared compounds

Tested compounds and standards (μg/mL, lot. no., bioanalyse)	Disc diffusion test (mm)[a]			
	Bacteria			
	Gram negative (*Escherichia coli*)	Gram positive (*Bacillus subtillis*)	Fungi (*Aspergillus nigrer*)	Yeast (*Candida albicans*)
Streptomycin (10,30225)	+++	+++	+	+++
Fusidic acid (10,30301)	—	—	+++	+++
1	+++	+++	+	++
2	+	+	+	+
3	+	+	—	—
4	++	++	+	+
5	+	+	—	—
6	+++	+++	++	++
7	+	+	—	—
8	+++	+++	+	++
9	+	—	—	—
10	++	+	—	+
11	+++	+++	—	+
12	+	+	+	+
13	+	+	—	—
14	+++	+++	+	+
15	+	+	—	—
16	+	+	—	+

[a]+++, highly sensitive (21–25 mm); ++, fairly sensitive (16–20 mm); +, slightly sensitive (15–10 mm); —, not sensitive (0–5 mm).

EXPERIMENTAL

All melting points were uncorrected and measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Microanalytical data were performed on a Vario El-Mentar apparatus (Shimadzu, Japan), National Research Centre, Cairo, Egypt. The IR spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrophotometer, National Research Centre, Cairo, Egypt. ^{1}H NMR and ^{13}C NMR spectra were determined on a Varian Mercury (300 MHz) spectrometer (Varian, UK), and the chemical shifts were expressed in parts per million (ppm) relative to tetramethylsilane (TMS) as internal reference, Faculty of Science, Cairo University, Egypt. Mass spectra were recorded on a 70-eV EI Ms-QP 1000 EX (Shimadzu, Japan), National Research Centre, Cairo, Egypt.

Compound **1** was prepared according to a reported method.[14]

2-Propyl-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (2)

An equimolar amount of compound **1** (0.23 g, 0.001 mol) and butyraldehyde (0.002 mol, 0.14 mL) in glacial acetic acid (30 mL) was refluxed for 10 h. The formed solid was filtered hot, dried, and recrystallized from dimethylformamide to give compound **2** (0.24 g, 85.71%); mp 228–230 °C. IR spectrum (KBr, ν, cm^{-1}): 3320 (NH), 1690 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.20 (t, $J = 7$ Hz, 3H, CH_3), 1.80 (m, 2H, CH_2), 2.60 (t, $J = 8$ Hz, 2H, CH_2), 3.80 (s, 2H, CH_2), 7.20–7.50 (m, 3H, Ar-H), 8.30 (d, $J = 9$ Hz, 1H, Ar-H), 12.30 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 13.8 (CH_3), 14.4 (CH_2), 35.30 (C-9), 36.6 (CH_2), 118.90–164.74 (Ar-C), 168.50 (C=O). MS, m/z (%): 282 (M^+, 100). Anal. calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 67.98; H, 5.04; N, 9.96; S, 11.29.

2-Phenyl-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (3)

Benzoyl chloride (0.002 mol, 0.29 mL) was added to a solution of compound **1** (0.23 g, 0.001 mol) in dry dioxane (50 mL) containing five drops of triethyl amine. The reaction mixture was heated for 3 h. The excess solvent was removed under reduced pressure, and the formed solid was recrystallized from dioxane to give compound **3** (0.19 g, 62.08%), mp 150–152 °C. IR spectrum (KBr, ν, cm^{-1}): 3421 (NH), 1699 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.80 (s, 2H, CH_2), 7.20–7.80 (m, 9H, Ar-H), 7.90 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 35.30 (C-9), 118.90–166.22 (Ar-C), 168.50 (C=O). MS, m/z (%): 316 (M^+, 100). Anal. calcd. for $C_{19}H_{12}N_2OS$: C, 72.13; H, 3.82; N, 8.85; S, 10.14. Found: C, 72.02; H, 3.90; N, 8.79; S, 10.21.

3,9-Dihydroindeno[1′,2′:4,5]thieno[2,3-*d*][1,2,3]triazin-4-one (4)

To a solution of compound **1** (0.23 g, 0.001 mol) in hydrochloric acid (20 mL) at 0–5 °C, a solution of sodium nitrite (0.10 g) in water (2 mL) was added over 20 min. Then the reaction mixture was stirred at 20–25 °C for 2 h, cooled, filtered off, dried, and recrystallized from dioxane to give compound **4** (0.19 g, 79%); mp 155–157 °C.

IR spectrum (KBr, ν, cm^{-1}): 3201 (NH), 1678 (C=O); ^1H NMR spectrum (DMSO-d_6, δ ppm): 4.10 (s, 2H, CH_2), 7.18–7.71 (m, 4H, Ar-H), 8.14 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 241 (M^+, 74). Anal. calcd. for $C_{12}H_7N_3OS$: C, 59.74; H, 2.92; N, 17.42; S, 13.29. Found: C, 59.82; H, 2.88; N, 17.37; S, 13.34.

Reaction of Compound 1 with Ethyl Chloroformate

Method A. Ethyl chloroformate (0.002 mol, 0.29 mL) was added to a solution of compound **1** (0.23 g, 0.001 mol) in dry dioxane (50 mL) containing five drops of triethyl amine. The reaction mixture was allowed to heat for 5 h, and the excess solvent was removed under reduced pressure. Then the remaining product was purified on silica gel at 60–80 °C using petroleum ether/ethyl acetate (70 mL/30 mL) to give compounds **5** (0.11 g, 43.60%) and **6** (0.12 g, 40.40%), respectively.

Method B. Ethyl chloroformate (0.002 mol, 0.29 mL) was added to a solution of compound **1** (0.23 g, 0.001 mol) in dry pyridine (50 mL). The reaction mixture was refluxed for 8 h, cooled, poured into water, neutralized with two or three drops of conc. hydrochloric acid (35%), filtered off, dried, and recrystallized from dioxane to give compound **5** (0.20 g, 78.12%). Compound **5** obtained from methods A and B has the same mp, 192–194 °C (mixed mp showed no depression).

Annulation of Compound 6 to 5

Compound **6** (0.10 g, 0.001 mol) was refluxed in 10 mL pyridine for 1 h, cooled, poured into water, neutralized with two or three drops of conc. hydrochloric acid (35%), filtered off, dried, and recrystallized from dioxane to give a compound (0.09 g, 69.23%) identical in all aspects with compound **5** (mp, mixed mp, TLC).

1,3,9-Trihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine-2,4-dione (5)

Mp 192–194 °C. IR spectrum (KBr, ν, cm^{-1}): 3340 (NH), 3333 (NH), 1717 (C=O), 1689 (C=O); ^1H NMR spectrum (DMSO-d_6, δ ppm): 4.17 (s, 2H, CH_2), 7.16–7.78 (m, 5H, Ar-H + NH, D_2O exchangeable), 10.14 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 35.30 (C-9), 120.12–156.24 (Ar-C), 164 (C=O), 168.50 (C=O). MS, m/z (%): 256 (M^+, 100). Anal. calcd. for $C_{13}H_8N_2O_2S$: C, 60.92; H, 3.15; N, 10.93; S, 12.51. Found: C, 61.01; H, 3.09; N, 11.00; S, 12.45.

(3-Carbamoyl-8*H*-indeno[2,1-*b*]thiophen-2-yl)-carbamic Acid Ethyl Ester (6)

Mp 99–101 °C. IR spectrum (KBr, ν, cm^{-1}): 3345, 3200 (NH_2), 3193 (NH), 1665 (C=O), 1710 (C=O); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.05 (t, $J = 8$ Hz, 3H, OCH_2CH_3), 3.90 (s, 2H, CH_2), 4.05 (q, $J = 9$ Hz, 2H, OCH_2CH_3), 7.30–7.70 (m, 6H, Ar-H + NH_2, D_2O exchangeable), 11.60 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 13.80 (CH_3), 35.30 (C-8), 56.9 (CH_2), 118.21–154.14 (Ar-C), 164.8 (C=O), 169.70 (C=O). MS, m/z (%): 302 (M^+, 64). Anal. calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27; S, 10.61. Found: C, 59.66; H, 4.59; N, 9.33; S, 10.54.

Synthesis of Compounds 7 and 8

Compound **1** (0.23 g, 0.001 mol) was added to dry pyridine (50 mL) containing phenyl isothiocyanate (0.001 mol, 0.26 mL). Then the reaction mixture was refluxed for 2 h, cooled, poured into water, neutralized with two or three drops of conc. hydrochloric acid (35%), filtered off, and dried, and the solid product was purified on silica gel at 60–80 °C using petroleum ether/ethyl acetate (70 mL/30 mL) to give compounds **7** (0.09 g, 25.86%) and **8** (0.17 g, 46.57%), respectively.

3-Phenyl-2-thioxo-1,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (7)

Mp 150–152 °C. IR spectrum (KBr, ν, cm^{-1}): 3202 (NH), 1650 (C=O), 1340 (C=S); ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.60 (s, 2H, CH_2), 7.14–7.49 (m, 9H, Ar-H), 9.82 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 35.30 (C-9), 118.90–146.75 (Ar-C), 164 (C=O), 170.50 (C=S). MS, m/z (%): 348 (M^+, 100). Anal. calcd. for $C_{19}H_{12}N_2OS_2$: C, 65.49; H, 3.47; N, 8.04; S, 18.41. Found: C, 65.56; H, 3.40; N, 8.11; S, 18.37.

2-(3-Phenyl-thioureido)-8*H*-indeno[2,1-*b*]thiophene-3-carboxylic Acid Amide (8)

Mp 120–122 °C. IR spectrum (KBr, ν, cm^{-1}): 3210–3115 (NH_2,NH), 1596 (C=O), 1327 (C=S); ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.60 (s, 2H, CH_2), 4.55 (s, 2H, NH_2, D_2O exchangeable), 7.20–7.70 (m, 10H, Ar-H + NH, D_2O exchangeable), 11.03 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 365 (M^+, 55). Anal. calcd. for $C_{19}H_{15}N_3OS_2$: C, 62.44; H, 4.14; N, 11.50; S, 17.55. Found: C, 62.36; H, 4.20; N, 11.44; S, 17.61.

3-Phenyl-1,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-2,4-dione (9)

Compound **8** (0.15 g, 0.001 mol) was refluxed in 10 mL ethanol containing 1 N potassium hydroxide (2 mL) for 1 h, cooled, poured into water, neutralized with two or three drops of conc. hydrochloric acid (35%), filtered off, dried, and recrystallized from dioxane to give compound **9** (0.12 g, 36.14%); mp 146–148 °C; IR spectrum (KBr, ν, cm^{-1}): 3333 (NH), 1642 (C=O), 1586 (C=O); ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.36 (s, 2H, CH_2), 6.80–7.32 (m, 9H, Ar-H), 8.36 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 34.62 (C-9), 119.20–156.74 (Ar-C), 164 (C=O), 170.50 (C=O). MS, m/z (%): 332 (M^+, 100). Anal. calcd. for $C_{19}H_{12}N_2O_2S$: C, 68.66; H, 3.64; N, 8.43; S, 9.65. Found: C, 68.71; H, 3.59; N, 8.50; S, 9.61.

2-Thioxo-1,3,9-trihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (10)

A solution of compound **1** (0.23 g, 0.001 mol) and potassium hydroxide (0.05 g, 0.001 mol) in ethanol (50 mL) was treated with carbon disulfide (5 mL), and the

reaction mixture was refluxed for 5 h. After removal of solvent under reduced pressure, the residual solid was dissolved in water (20 mL) and acidified with hydrochloric acid (2 mL, 10%). The separated solid was filtered off, dried, and recrystallized from ethanol to give compound **10** (0.23 g, 86.14%); mp 240–242 °C. IR spectrum (KBr, ν, cm^{-1}): 3345 (NH), 3330 (NH), 1665 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.20–3.40 (bs, 1H, SH, D_2O exchangeable), 3.90 (s, 2H, CH_2), 7.20–7.55 (m, 4H, Ar-H), 12.52 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 33.56 (C-9), 119.30–152.16 (Ar-C), 162 (C=O). MS, m/z (%): 272 (M^+, 100). Anal. calcd. for $C_{13}H_8N_2OS_2$: C, 57.33; H, 2.96; N, 10.29; S, 23.55. Found: C, 57.42; H, 3.00; N, 10.21; S, 23.44.

2,10-Dihydroindeno[1′,2′:4,5]thieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidine-3,5-dione (11)

A mixture of compound **10** (0.27 g, 0.001 mol) and chloroacetic acid (0.10 g, 0.001 mol) was refluxed in a mixture of glacial acetic acid/acetic anhydride (30 mL/10 mL) containing anhydrous sodium acetate (0.25 g, 0.005 mol) for 3 h. The reaction mixture was cooled and poured into water, and the formed solid was filtered off, dried, and recrystallized from dimethyl formamide (DMF) to give compound **11** (0.17 g, 55.60%); mp 204–206 °C. IR spectrum (KBr, ν, cm^{-1}): 1685 (C=O), 1703 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.90 (s, 2H, CH_2), 4.20 (s, 2H, CH_2), 7.20–7.50 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6, δ ppm): 35.30 (C-10), 42.12 (C-2), 118.10–146.24 (Ar-C), 168 (C=O), 170.50 (C=O). MS, m/z (%): 312 (M^+, 100). Anal. calcd. for $C_{15}H_8N_2O_2S_2$: C, 57.68; H, 2.58; N, 8.97; S, 20.53. Found: C, 57.74; H, 2.65; N, 8.89; S, 20.44.

2-Methylsulfanyl-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (12)

A solution of compound **10** (0.27 g, 0.001 mol) and potassium hydroxide (0.05 g, 0.001 mol) in ethanol (50 mL) was treated with methyl iodide (0.001 mol, 0.16 mL), and the reaction mixture was warmed on a steam bath at 70 °C for 2 h. The formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound **12** (0.25 g, 88.50%); mp 160–162 °C. IR spectrum (KBr, ν, cm^{-1}): 3345 (NH), 1665 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.40 (s, 3H, SCH_3), 3.77 (s, 2H, CH_2), 7.21–7.34 (m, 4H, Ar-H), 7.51 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 12.10 (CH_3), 34.46 (C-9), 118.62–164.12 (Ar-C), 170.50 (C=O). MS, m/z (%): 286 (M^+, 92). Anal. calcd. for $C_{14}H_{10}N_2OS_2$: C, 58.72; H, 3.52; N, 9.78; S, 22.39. Found: C, 58.79; H, 3.48; N, 9.84; S, 22.42.

2-Hydrazino-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-4-one (13)

A mixture of compound **12** (0.28 g, 0.001 mol) and hydrazine hydrate 99% (0.004 mol, 1 mL) was refluxed in ethanol (50 mL) for 3 h. The reaction mixture was evaporated under reduced pressure, and the formed solid was filtered off, dried, and recrystallized from ethanol to give **13** (0.19 g, 70.40%); mp 180–182 °C. IR spectrum (KBr, ν, cm^{-1}): 3250–3110 (NH_2,NH), 1696 (C=O); ^{1}H NMR spectrum

($CDCl_3$, δ ppm): 3.82 (s, 2H, NH_2, D_2O exchangeable), 3.94 (s, 2H, CH_2), 7.18–7.45 (m, 5H, Ar-H, NH, D_2O exchangeable), 9.85 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 270 (M^+, 84). Anal. calcd. for $C_{13}H_{10}N_4OS$: C, 57.76; H, 3.73; N, 20.73; S, 11.86. Found: C, 57.82; H, 3.68; N, 20.78; S, 11.79.

1,10-Dihydroindeno[1′,2′:4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (14)

Compound **13** (0.27 g, 0.001 mol) was refluxed in formic acid (20 mL) for 15 h, then the reaction mixture was poured into water, and the formed solid was filtered off, dried, and recrystallized from ethanol to give **14** (0.16 g, 58.57%), mp 250–252 °C. IR spectrum (KBr, ν, cm^{-1}): 3334 (NH), 1643 (CO); ^1H NMR spectrum ($CDCl_3$, δ ppm): 3.36 (s, 2H, CH_2), 6.90 (s, 1H, C_3-H), 7.24–7.54 (m, 4H, Ar-H), 9.85 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 36.58 (C-10), 119.45–164.32 (Ar-C), 170.50 (C=O). MS, m/z (%): 280 (M^+, 100). Anal. calcd. for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99; S, 11.44. Found: C, 60.03; H, 2.95; N, 19.89; S, 11.38.

(4-Oxo-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-2-ylsulfanyl)-acetic Acid Ethyl Ester (15)

A solution of compound **10** (0.27 g, 0.001 mol) and potassium hydroxide (0.5 g, 0.001 mol) in ethanol (50 mL) was treated with ethyl chloroacetate (0.001 mmol, 0.13 mL), and the reaction mixture was stirred at room temperature for 3 h. The formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound **15** (0.35 g, 98.50%), mp 101–103 °C. IR spectrum (KBr, ν, cm^{-1}): 3225 (NH), 1732 (C=O). ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.38 (t, $J = 7$ Hz, 3H, OCH_2CH_3), 3.26 (q, $J = 9$ Hz, CH_2), 3.55 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 7.16–7.51 (m, 4H, Ar-H), 7.88 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 13.74 (CH_3), 33.95 (CH_2S), 35.30 (C-9), 61.12 (CH_2O), 119.90–145.50 (Ar-C), 168.11 (C=O), 170.50 (C=O). MS, m/z (%): 358 (M^+, 65). Anal. calcd. for $C_{17}H_{14}N_2O_3S_2$: C, 56.96; H, 3.94; N, 7.82; S, 17.89. Found: C, 57.01; H, 4.01; N, 7.75; S, 17.82.

(4-Oxo-3,9-dihydroindeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-2-ylsulfanyl)-acetic Acid Hydrazide (16)

Hydrazine hydrate (1 mL, 99%) was added to a solution of compound **15** (0.35 g, 0.001 mol) in ethanol (50 mL), and the reaction mixture was heated on a water bath for 5 h. After cooling, the precipitated material was filtered off, washed with water, dried, and recrystallized from dioxane to give compound **16** (0.33 g, 96%), mp 230–232 °C. IR spectrum (KBr, ν, cm^{-1}): 3422–3245 (NH_2, NH), 1696 (C=O), 1634 (C=O). ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.64 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 5.47 (bs, 2H, NH_2, D_2O exchangeable), 7.09–7.55 (m, 5H, Ar-H, NH, D_2O exchangeable), 9.40 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 344 (M^+, 65). Anal. calcd. for $C_{15}H_{12}N_4O_2S_2$: C, 52.31; H, 3.51; N, 16.27; S, 18.62. Found: C, 52.40; H, 3.45; N, 16.30; S, 18.58.

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