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Synthesis of Some New Substituted Thieno[2,3-*d*]pyrimidine Derivatives as Antimicrobial Agents

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Abstract—A series of thieno-pyrimidine derivatives are synthesized from 5'-amino-2,3'-bithiophene-4'-carboxylate via the corresponding intermediate *N*-benzoylated carboxamide derivatives. The target compounds are tested for antibacterial and antifungal activity. Some of the synthesized compounds demonstrate potent antibacterial activity with LD_{50} comparable with the reference drug indomethacin.

Keywords: thiophene moiety, thieno[2,3-*d*]pyrimidines derivatives, antimicrobial activity

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Thiophene and its derivatives are distinguished as important structural components of some drugs [1–6] and active antitumor [7], antiviral [8], antimicrobial [9–14], and anti-inflammatory [15, 16] compounds. Based on these facts and in continuation of our recent studies in heterocyclic chemistry [17–21], we have synthesized novel thieno[2,3-*d*]-pyrimidin-4(3*H*)-ones, 3-(4-substituted benzylideneamino) and benzoylhydrazinecarbonyl derivatives for testing their antibacterial and cytotoxic activities.

RESULTS AND DISCUSSION

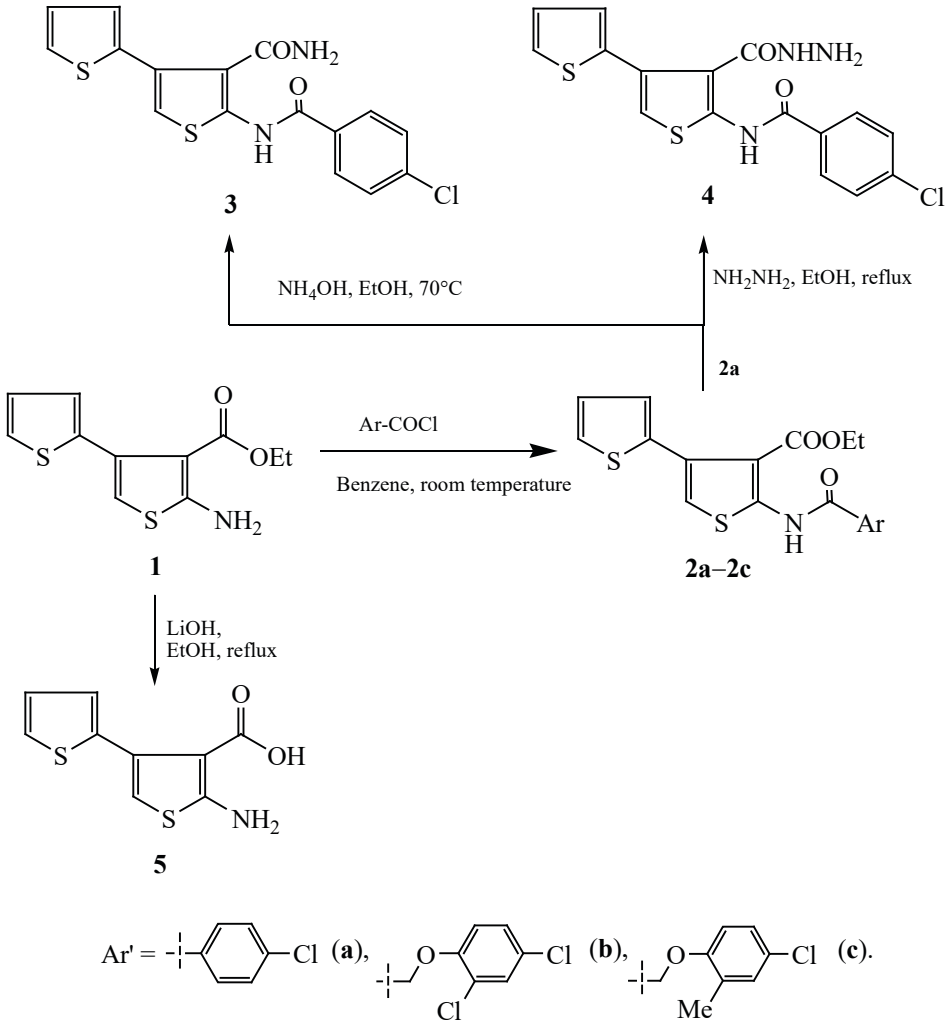
Ethyl 5'-amino-2,3'-bithiophene-4'-carboxylate (**1**), synthesized from the corresponding 2-acetylthiophene [14], reacted with a benzoyl chloride to give the corresponding *N*-benzoylated derivatives **2a**–**2c** (Scheme 1). Presence of the 4'-ethylcarboxylate group in compounds **2a**–**2c** made these to act as versatile precursors for the synthesis of 4'-carboxamide (**3**) and 4'-hydrazinecarbonyl **4** derivatives.

Refluxing of compound **3** under basic conditions led to the product of cyclization **6** in good yield. Generally, compound **6** can be regarded as an active intermediate leading to formation of 4-chlorothienopyrimidine derivative **7,** which upon reaction with secondary amines, gave the corresponding 4-substituted morpholine **8** and 4-hydrazine **9** derivatives. The compound **9** was treated with phenyl isothiocyanate with formation of phenylhydrazine carbothioamide derivative **10** in poor yield (Scheme 2).

Thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivative (**11**) was obtained either by refluxing compound **2a** with hydrazine hydrate in butanol, or refluxing 4'-hydrazinecarbonyl derivative **4** in butanol. The Schiff bases **12a**, **12b** were produced by condensation of **11** with an aldehyde, 4-chlorobenzaldehyde or 4-nitrobenzaldehyde under refluxing in isopropanol containing a catalytic amount of glacial acetic acid (Scheme 3).

Antimicrobial activity. The compounds **3**–**12** were tested for their *in-vitro* antimicrobial activity against gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and gram-negative *Escherichia coli* bacteria using antibiotic Ciprofloxacin (50 μg /mL) as a reference drug, and fungi (*Aspergillus flavus* and *Candida albicans*) using antibiotic Fusidic acid (50 μg /mL). The compounds were tested in concentration of 50 μg/mL using inhibi-

Scheme 1. Synthetic roots to compounds **2**–**5.**



tion zone diameter (mm) as a criterion of antimicrobial activity (see the table).

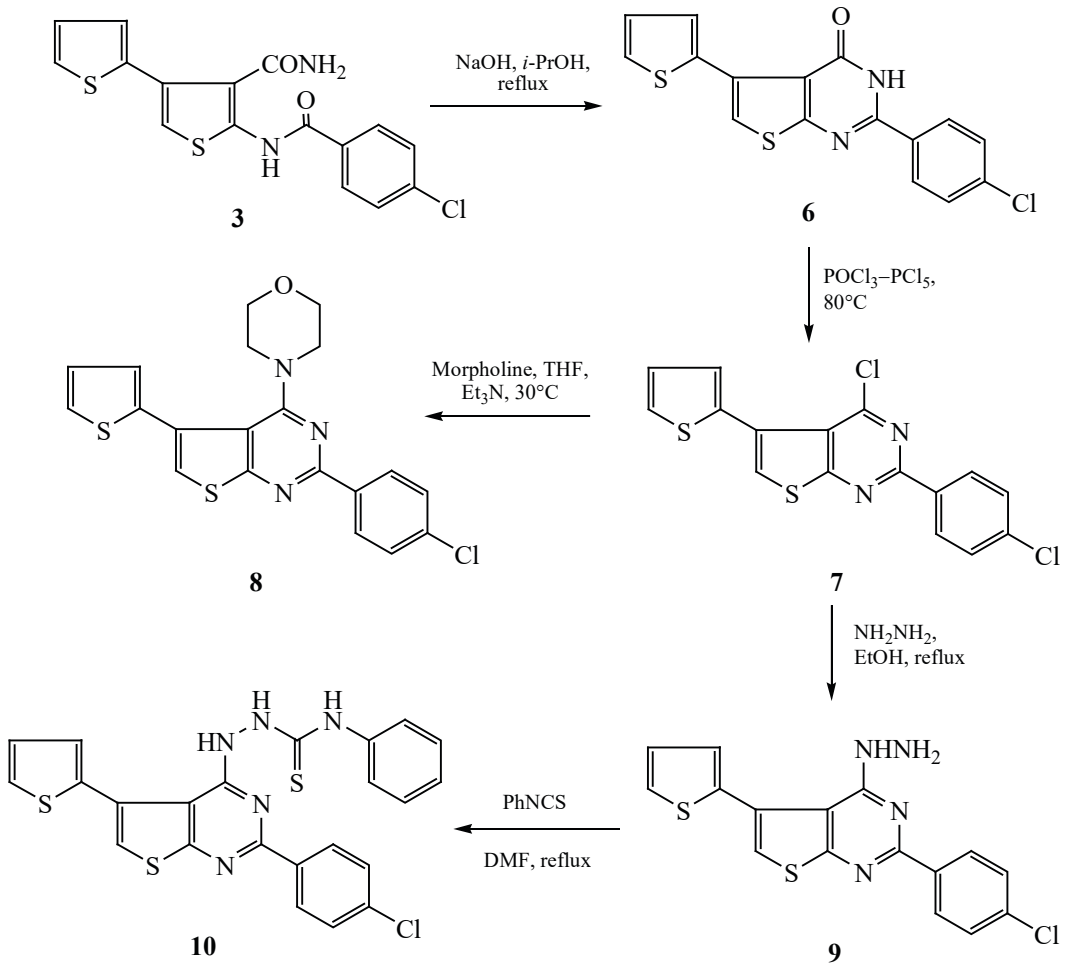
EXPERIMENTAL

Melting points were determined in open glass capillary tubes on an Electro Thermal Digital melting point apparatus (model: IA9100), and are uncorrected. CHN microanalysis was carried out on a Microanalytical Unit, NRC. FTIR spectra were recorded on a Nexus 670 FTIR Nicolet spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Jeol 500 MHz (^{1}H) and 125 MHz (^{13}C) spectrometer using DMSO-d_6 as a solvent. Mass spectra were measured on a MAT Finnigan SSQ 7000 spectrometer, using the electron impact technique (EI). TLC was performed on silica gel aluminum sheets, 60 F_{254} (E. Merck).

Synthesis of ethyl 5'-(substituted phenyl)-2,3'-bithiophene-4'-carboxylate (2a–2c). A mixture of equimolar amounts of compound **1** (0.01 mol) and an appropriate acid chloride (0.01 mol) in dry benzene (10 mL) was stirred for 3 h. The separated solid was filtered off, washed with petroleum ether 60–80 and crystallized from ethanol to give the corresponding compounds **2a**–**2c**.

Ethyl 5'-(4-chlorobenzamido)-2,3'-bithiophene-4'-carboxylate (2a). Yield 77%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 3250 (NH), 1725, 1655 (2C=O). ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3 ethyl), 4.22 q (2H, CH_2 ethyl), 7.08–7.98 m (8H, Ar-H and thiophene-H), 11.95 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 14.30 (CH_3), 61.23 (CH_2), 113.35, 118.39, 126.19, 127.25, 127.69, 129.70, 129.83, 131.18, 131.65, 137.56, 138.32, 145.94, 162.99, 165.32. MS: *m/z:* 391 $[M]^+$. Found, %: C 55.11; H 3.49; N 3.49. $C_{18}H_{14}ClNO_3S_2$. Calculated, %: C 55.17; H 3.60; N 3.57.

Scheme 2. Synthetic roots to compounds **6**–**10**.

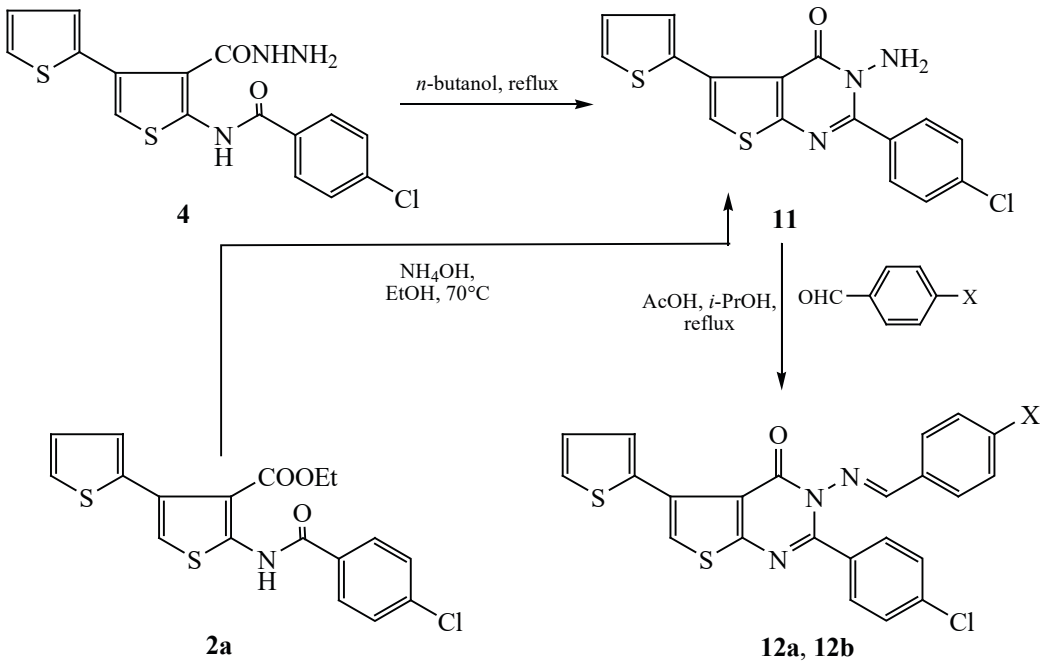


Ethyl 5'-[2-(2,4-dichlorophenoxy)acetamido]-2,3'-bithiophene-4'-carboxylate (2b). Yield 85%, mp: 218–220°C. IR spectrum, ν, cm^{-1}: 3245 (NH), 1730, 1659 (2C=O). ^{1}H NMR spectrum, δ, ppm: 1.04 t (3H, CH_3 ethyl), 4.14 q (2H, CH_2 ethyl), 5.06 s (2H, CH_2), 7.10–7.68 m (7H, Ar-H and thiophene-H), 11.66 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 14.30, 61.23, 112.05, 116.32, 121.31, 126.05, 127.21, 128.05, 128.11, 129.14, 130.54, 131.52, 132.93, 136.26, 139.37, 144.08, 163.72, 166.10, 178.32. MS: *m/z:* 456 [*M*]$^+$. Found, %: C 49.88; H 3.25; N 3.00. $C_{19}H_{15}Cl_2NO_4S_2$. Calculated, %: C 50.01; H 3.31; N 3.07.

Ethyl 5'-[2-(4-chloro-2-methylphenoxy]acetamido)-2,3'-bithiophene-4'-carboxylate (2c). Yield 65%, mp: 204-206°C. IR spectrum, ν, cm^{-1}: 3255 (NH), 1727, 1658 (2C=O). ^{1}H NMR spectrum, δ, ppm: 1.03 t (3H, CH_3 ethyl), 2.11 t (3H, CH_3), 4.15 q (2H, CH_2 ethyl), 4.94 q (2H, CH_2), 6.68–7.55 m (7H, Ar-H and thiophene-H), 11.81 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ, ppm: 13.76, 62.71, 75.52, 115.51, 117.32, 120.65, 124.22, 125.58, 127.43, 127.85, 129.31, 131.65, 131.99, 132.92, 135.83, 137.44, 143.81, 164.80, 169.72, 173.21. MS: *m/z:* 435 [*M*]$^+$. Found, %: C 55.00; H 4.06; N 3.15. $C_{20}H_{18}ClNO_4S_2$. Calculated, %: C 55.10; H 4.16; N 3.21.

Synthesis of 5'-(4-chlorobenzamido)-2,3'-bithiophene-4'-carboxamide (3). To a solution of compound **2a** (0.01 mol) in ethanol (30 mL), ammonia solution (20 mL, 50%) was added. The reaction mixture was heated to 70ºC upon stirring for 8 h. The formed precipitate was filtered off, washed with water, and crystallized from ethanol to give compound **3**. Yield 75%, mp: 186–188°C. IR spectrum, ν, cm^{-1}: 3450–3190 (NH, NH_2), 1680, 1667 (2C=O). ^{1}H NMR spectrum, δ, ppm: 4.12 br.s (2H, NH_2, exchangeable with D_2O), 6.34–7.98 m (8H, Ar-H and thiophene-H), 11.95 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 115.71, 124.93, 126.42, 127.74, 128.80, 129.33, 131.12,

Scheme 3. Synthetic roots to compounds **11** and **12.**



X = Cl (**a**), NO_2 (**b**).

131.96, 135.52, 139.14, 140.37, 144.18, 163.27, 169.39. MS: *m/z:* 362 $[M]^+$. Found, %: C 52.87; H 3.00; N 7.64. $C_{16}H_{11}ClN_2O_2S_2$. Calculated, %: C 52.96; H 3.06; N 7.72.

Synthesis of 4-chloro-*N*-(4'-(hydrazinecarbonyl)-2,3'-bithiophen-5'-yl)benzamide (4). A mixture of compound **2a** (0.01 mol) with hydrazine hydrate (15 mL; 0.03 mol) in ethanol (20 mL) was refluxed for 6 h, then concentrated to half of its volume and cooled down to room temperature. A white crystalline product was crystallized from ethanol to give compound **4**. Yield 60%, mp: 165–167°C. IR spectrum, ν, cm^{-1}: 3438–3250 (2NH, NH_2), 1680, 1665 (2C=O). ^1H NMR spectrum, δ, ppm: 4.37 br.s (2H, NH_2, exchangeable with D_2O), 6.67 br.s (1H, NH, exchangeable with D_2O), 7.08–7.98 m (8H, Ar-H and thiophene-H), 12.01 br.s (2H, 2NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 116.75, 127.65, 128.34, 129.73, 130.06, 130.06, 130.59, 132.12, 135.82, 136.19, 139.10, 141.06, 162.69, 165.71. MS: *m/z:* 377 $[M]^+$. Found, %: C 50.72; H 3.12; N 11.08. $C_{16}H_{12}ClN_3O_2S_2$. Calculated, %: C 50.86; H 3.20; N 11.12.

Synthesis of 5'-amino-2,3'-bithiophene-4'-carboxylic acid (5). Compound **1** (0.01 mol) was added to a solution of LiOH (0.01 mol) in EtOH–H_2O (1 : 1.5, 50 mL) and refluxed for 1 h. Upon cooling down the reaction mixture was poured into 50 mL of cold water and treated with 1N HCl to pH 4–5. The solid formed was filtered off and recrystallized from ethanol to give compound **5**. Yield 60%, mp 112–114°C. IR spectrum, ν, cm^{-1}: 3450 (OH), 3250 (NH_2), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 7.07–7.85 m (8H, Ar-H, NH_2 and thiophene-H), 12.36 br.s,(1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 102.13, 111.87, 124.27, 125.00, 128.07, 130.37, 132.23, 164.72, 167.78. MS: *m/z:* 225 $[M]^+$. Found, %: C 47.87; H 3.05; N 6.16. $C_9H_7NO_2S_2$. Calculated, %: C 47.98; H 3.13; N 6.22.

Synthesis of 2-(4-chlorophenyl)-5-(thiophen-2-yl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-one (6). To a solution of compound **3** (0.01 mol) in isopropanol (50 mL) was added 5% solution of NaOH (0.1 mol), and the mixture was refluxed for 3 h. After cooling down, the reaction mixture was poured into ice cold water upon stirring, and acidified with HCl to pH 5–6. The residue was filtered off, dried and crystallized from butanol to give compound **6**. Yield 59%, mp 208–210°C. IR spectrum, ν, cm^{-1}: 3460 (NH), 1670 (CO). ^1H NMR spectrum, δ, ppm: 7.01–7.23 m (8H, Ar-H and thiophene-H), 11.21 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 114.67, 117.20, 124.79, 126.27, 128.20, 128.60, 130.55,

Anti-microbial activity of the synthesized compounds

Compound	Diameter of inhibition zone, mm[a]				
	+ve bacteria		–ve bacteria	fungi	
	S. aureus	*B. subtitls*	*E. coli*	*A. flavus*	*C. albicans*
4	17	14	14	12	15
5	19	20	15	15	20
6	15	13	9	21	14
7	14	17	20	13	16
8	22	19	16	18	17
9	20	21	21	22	21
10	21	20	20	19	19
11	14	9	6	13	12
12	13	7	22	9	22
Ciprofloxacin[b]	20	21	21	23	23
Fusidic acid	14	19	11	16	18

[a] (≥15 mm) no inhibition, (16–20 mm) moderate inhibition, (≥20 mm) maximum inhibition.

[b] Standard drug concentration 50 μg/mL.

136.01, 138.45, 145.61, 153.63, 159.10, 164.59, 166.47. MS: *m/z:* 344 $[M]^+$. Found, %: C 55.65; H 2.56; N 8.05. $C_{16}H_9ClN_2OS_2$. Calculated, %: C 55.73; H 2.63; N 8.12.

Synthesis of 4-chloro-2-(4-chlorophenyl)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidine (7). To a solution of compound **6** (5 mmol) in phosphorus oxychloride (10 mL) was added a mixture of phosphoric anhydride (5 mmol) with phosphorus oxychloride (5 mL). The reaction mixture was refluxed for 4 h. After cooling down, it was poured onto water with crushed ice and neutralized by 5% NaOH solution. The precipitate was filtered off, washed with water and crystallized from ethanol to give compound **7**. Yield 70%, mp 168–170°C. ^{1}H NMR spectrum, δ, ppm: 7.06–8.17 m (8H, Ar-H and thiophene-H). ^{13}C NMR spectrum, δ_C, ppm: 114.74, 117.98, 125.00, 126.40, 128.12, 128.65, 129.98, 136.60, 138.26, 146.53, 151.53, 158.65, 164.78, 166.93. MS: *m/z:* 363 $[M]^+$. Found, %: C 52.80; H 2.12; N 7.63. $C_{16}H_8Cl_2N_2S_2$. Calculated, %: C 52.90; H 2.22; N 7.71.

Synthesis of 4-{2-(4-chlorophenyl)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidin-4-yl}morpholine (8). Triethylamine (0.026 mol) and morpholine (0.019 mol) were added to a solution of compound **7** (0.017 mol) in THF (80 mL). After stirring for 2 h at 30°C, the excess of THF was removed under reduced pressure. The residual mixture was poured into water (200 mL), the precipitate was filtered off to give compound **8**. Yield 65%, mp 132–134°C. ^{1}H NMR spectrum, δ, ppm: 2.08 t (4H, $2CH_2N$), 3.18 t (4H, $2CH_2O$), 6.90–8.52 m (8H, Ar-H and thiophene-H). ^{13}C NMR spectrum, δ_C, ppm: 31.16, 39.63, 40.34, 115.68, 116.45, 119.58, 123.66, 124.81, 125.54, 126.22, 128.89, 129.04, 130.46, 132.16, 137.50, 138.57, 162.79, 164.67, 165.46, 179.82. MS: *m/z:* 413 $[M]^+$. Found, %: C 57.96; H 3.82; N 10.06. $C_{20}H_{16}ClN_3OS_2$. Calculated, %: C 58.03; H 3.90; N 10.15.

Synthesis of 2-(4-chlorophenyl)-4-hydrazinyl-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidine (9). A mixture of compound **7** (0.01 mol) with hydrazine hydrate (15 mL, 0.03 mol) in ethanol (20 mL) was refluxed for 6 h, then concentrated to half of its volume and cooled down to room temperature. A white crystalline product was crystallized from ethanol. Yield 60%, mp 162–164°C. IR spectrum, ν, cm^{-1}: 3430, 3250 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm: 3.73 br.s (2H, NH_2, exchangeable with D_2O), 7.11–7.97 m (8H, Ar-H and thiophene-H), 11.10 br.s (1H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ, ppm: 116.93, 116.96, 121.96, 125.56, 126.24, 128.19, 130.45, 137.20, 137.50, 138.52, 144.32, 145.06,

163.68, 164.27. MS: *m/z:* 358 [*M*]$^+$. Found, %: C 53.40; H 3.00; N 15.55. $C_{16}H_{11}ClN_4S_2$. Calculated, %: C 53.55; H 3.09; N 15.61.

Synthesis of 2-{2-(4-chlorophenyl)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidin-4-yl}-*N*-phenyl-hydrazine carbothioamide (10). A mixture of compound **9** (0.01 mol) with phenyl isothiocyanate (0.01 mol) in DMF (20 mL) was refluxed for 2 h. The obtained precipitate was filtered off and crystallized from *n*-butanol to give compound **10**. Yield 55%, mp 112–114°C. IR spectrum, ν, cm^{-1}: 3420–3215 (3NH). ^{1}H NMR spectrum, δ, ppm: 7.08–7.96 m (13H, Ar-H and thiophene-H), 10.41 s, 11.08 s, 11.92 s (3H, 3NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 123.66, 124.81, 125.54, 126.22, 127.85, 128.19, 128.78, 128.90, 129.04, 129.19, 130.46, 132.16, 137.19, 138.57, 162.79, 164.29, 164.67, 165.46, 179.82. MS: *m/z:* 493 [*M*]$^+$. Found, %: C 55.80; H 3.18; N 14.08. $C_{23}H_{16}ClN_5S_3$. Calculated, %: C 55.92; H 3.26; N 14.18.

Synthesis of 3-amino-2-(4-chlorophenyl)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (11). *a*. A mixture of compound **2a** (0.02 mol) with hydrazine hydrate 95% (5.01 g, 0.1 mol) were refluxed in butanol (10 mL) for 8 h. Addition of ethanol (2 mL) to the reaction mixture gave the product as white precipitate, which was filtered off and recrystallized from aqueous ethanol to give compound **11**.

b. Compound **4** (0.02 mol) was refluxed in butanol (10 mL) for 24 h. The excess solvent was distilled off and the solid residue was air dried and then recrystallized from aqueous ethanol to give compound **11**. Yield 60%, mp 253–255°C. IR spectrum, ν, cm^{-1}: 3260 (NH_2), 1665 (CO). ^{1}H NMR spectrum, δ, ppm: 5.70 br.s (2H, NH_2 exchangeable with D_2O), 7.15–7.89 m (8H, Ar-H and thiophene-H). ^{13}C NMR spectrum, δ_C, ppm: 118.20, 122.04, 127.77, 128.09, 131.07, 132.17, 130.07, 133.39, 135.22, 136.52, 155.28, 158.05, 164.01, 164.03. MS: *m/z:* 359 [*M*]$^+$. Found, %: C 53.30; H 2.72; N 11.60. $C_{16}H_{10}ClN_3OS_2$. Calculated, %: C 53.40; H 2.80; N 11.68.

Synthesis of compounds 12a, 12b. A mixture of compound **5** (0.01 mol) with an appropriate aryl aldehyde (0.01 mol) in isopropanol containing glacial acetic acid (2 mL) was refluxed for 2 h. Upon cooling down, the precipitate was filtered off and crystallized from methanol to give the corresponding compound **12a** or **12b.**

3-(4-Chlorobenzylideneamino)-2-(4-chlorophenyl)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (12a). Yield 67%, mp 244–246°C. IR spectrum, ν, cm^{-1}: 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.71 s (1H, CH=N), 7.13–7.89 m (12H, Ar-H and thiophene-H). ^{13}C NMR spectrum, δ_C, ppm: 118.20, 118.56, 122.04, 126.87, 127.77, 128.09, 128.53, 129.08, 132.17, 135.23, 135.25, 136.51, 136.54, 138.10, 155.28, 155.30, 158.05, 158.07, 164.01. MS: *m/z:* 482 [*M*]$^+$. Found, %: C 57.15; H 2.65; N 8.60. $C_{23}H_{13}Cl_2N_3OS_2$. Calculated, %: C 57.27; H 2.72; N 8.71.

2-(4-Chlorophenyl)-3-(4-nitrobenzylideneamino)-5-(thiophen-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (12b). Yield 60%, mp 261-263°C. IR spectrum, ν, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.73 s (1H, CH=N), 7.16–7.92 m (12H, Ar-H and thiophene-H). ^{13}C NMR spectrum, δ_C, ppm: 119.04, 119.82, 123.06, 124.95, 126.40, 128.57, 128.74, 129.17, 133.55, 134.96, 135.05, 136.86, 137.51, 150.45, 156.54, 156.30, 157.60, 159.57, 164.62. MS: *m/z:* 493 [*M*]$^+$. Found, %: C 55.95; H 2.58; N 11.29. $C_{23}H_{13}ClN_4O_3S_2$. Calculated, %: C 56.04; H 2.66; N 11.37.

Antimicrobial activity. Antimicrobial activity of the synthesized compounds was determined by the agar diffusion method [22, 23].

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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