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Research Article

Synthesis, Characterization, and Antibacterial and Anti-Inflammatory Activities of New Pyrimidine and Thiophene Derivatives

Siham Lahsasni,[1] **Dunya A. M. Al-Hemyari**,[1] **Hazem A. Ghabbour**,[2,3] **Yahia Nasser Mabkhoot**,[1] **Fadilah S. Aleanizy**,[1] **Asma A. Alothman**,[1] **and Zainab M. Almarhoon**[1]

[1]*Department of Chemistry, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[2]*Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia*
[3]*Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt*

Correspondence should be addressed to Siham Lahsasni; slahsasni@ksu.edu.sa

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Substituted[4,5]thieno[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (**3a–b**) and pyrimidin-5(6*H*)-imine (**3c–e**) were synthesized via reaction of the starting compounds, ethyl 2-amino-substituted[*b*]thiophene-3-carboxylate (**2a–c**) and 2-amino-substituted [*b*]thiophene-3-carbonitrile (**2d–f**), respectively, with 2-bromothiazole. Synthesis of (bromo-substituted[*b*]thiophen-2-yl) alkanamide derivatives (**4a–e**) and thieno[2,3-*d*][1,3]oxazin-4-imine derivative (**5**) was accomplished via reaction of the starting compounds with bromoalkyl chloride through nucleophilic substitution; however, for the synthesis of compound **5**, nucleophilic substitution was followed by nucleophilic addition to a nitrile group to form the oxazinimine ring. 1-(3-cyano-substituted[*b*]thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea derivatives (**6a–c**) were obtained via reaction of the starting compounds (**2d–f**) and 4-(trifluoromethyl phenyl)isothiocyanate. The lead compounds (**2d–f**) rapidly reacted with 4-(trifluoromethyl)benzaldehyde or 4-(2-pyridyl)benzaldehyde in acidic medium to yield compounds (**7a–f**) in large quantities. X-ray crystallography of compounds **4c** and **7e** confirmed their structures. Antimicrobial studies revealed that compound **6a** was equally potent to ampicillin against *Bacillus* strains. Moreover, compounds **3e**, **4d**, and **6a** possessed greater anti-inflammatory potency than that of the standard drug.

1. Introduction

Thiophene, thiazole, and pyrimidine derivatives have been used as therapeutic drugs over years. Figure 1 shows some potent drugs containing thiazole or thiophene ring.

Dasatinib is a dual Src/Abl [1] and *pan*-Src [2] kinase inhibitor, zopolrestat [3] and lidorestat [4] are aldose reductase inhibitors used for the treatment of diabetic complications, and raloxifene is the first clinically available selective estrogen receptor modulator (SERM) used to prevent both osteoporosis and breast cancer [5–8]. In addition, clopidogrel is an antiplatelet agent used to inhibit blood clots in coronary artery disease and to prevent heart attacks and strokes in patients with heart or circulatory diseases [9–11].

The most efficient protocol for the synthesis of these thiophene derivatives is intramolecular cyclization via nucleophilic displacement [12–15], Gewald method [16, 17], thio-Claisen rearrangement [18], and dehydrophotocyclization [19, 20].

Within the scope of these diverse synthetic methods and utility of thiophene-based systems and in continuation to our interest in the design of bioactive heterocycles [21–23], we aimed at developing novel heterocyclic compounds containing thiophene, thiazole, and pyrimidine rings, identifying their structures using infrared (IR), ^{1}H nuclear

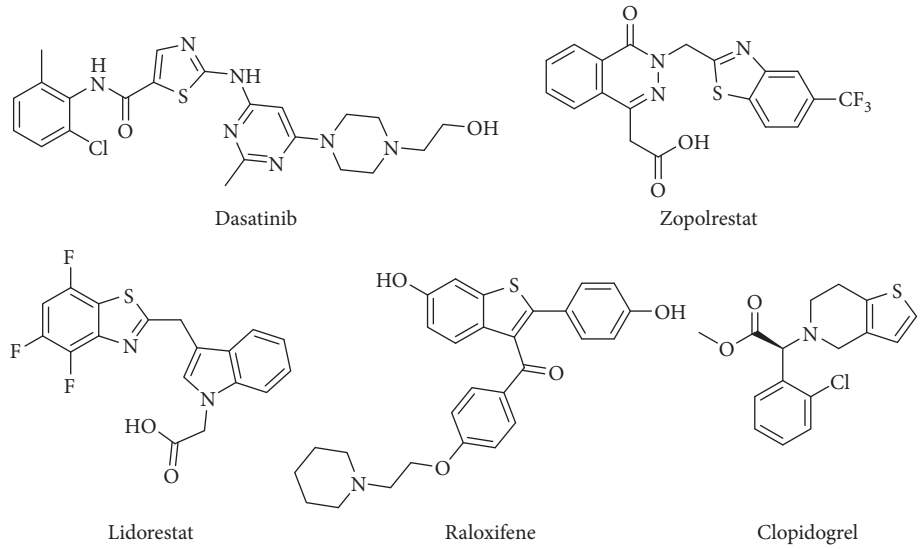


Figure 1: Some drugs containing thiazole, pyrimidine, or thiophene ring.

magnetic resonance (^{1}H NMR), ^{13}C NMR spectroscopy, and X-ray, and evaluating their biological effects, in particular, their antimicrobial and anti-inflammatory activities.

2. Materials and Methods

2.1. General Information. Melting points (mp) were determined using an electrothermal digital melting point apparatus and were uncorrected. IR spectra (KBr discs) were recorded using FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were recorded using Varian Gemini-200 (200 MHz) and Jeol AS (500 MHz) instruments. Dimethyl sulfoxide- (DMSO-) *d*6 was used as a solvent, and tetramethylsilane (TMS) was used as an internal standard. Chemical shifts were expressed as δ ppm. Mass spectra were recorded using Hewlett Packard 5988 A GC/MS system and GCMS-QP 1000 Ex Shimadzu instrument. Vario EL III Elemental CHNS analyzer at the Microanalytical Data Unit of Cairo University was used to obtain the analytical data.

2.2. Chemistry

*2.2.1. Synthetic Procedure for Substituted [4,5]Thieno[2,3-d] thiazolo[3,2-a]pyrimidine Derivatives (**3a–e**).* A mixture of the appropriate lead compound (**2b–f**) (5 mmol), an excess amount of 2-bromothiazole (approximately 1 mL), and few drops of hydrochloric acid in absolute ethanol (3 mL) was refluxed for 3–5 h. The product started to precipitate shortly once the reaction started (within approximately 15 min). The precipitate was filtered, washed with absolute ethanol, dried, and recrystallized from absolute ethanol.

*6,7,8,9-Tetrahydro-5H-benzo[4,5]thieno[2,3-d]thiazolo[3,2-a]pyrimidin-5-one (**3a**).* White solid; yield: 30%; mp: 221–222°C; IR (KBr, υ_{max}, cm^{-1}): 3079.1 (CH aromatic), 2930.47 (CH aliphatic), 1675.45 (C=O), and 1563.55, 1516.11 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.878 (*m*, 4H, *J* = 6 Hz, H7-8), 2.77 (*t*, 2H, *J* = 6 Hz, H9), 3.049 (*t*, 2H, *J* = 6 Hz, H6), 6.87 (*d*, 1H, *J* = 4.8 Hz, H2), and 7.98 (*d*, 1H, *J* = 4.8 Hz, H3); ^{13}C NMR (δ, ppm, $CDCl_3$): 22.253, 22.95, 25.158, 25.618 (C6-9), 109.571 (C2), 116.155 (C5a), 121.652 (C5a′), 130.973 (C3), 131.479 (C9a), 154.951 (C10a), 157.419 (C11a), and 163.835 (C5); and DART-TOF-MS (*m/z*): 263.03 $[M + H]^+$; anal. calcd. for $C_{12}H_{10}N_2OS_2$ (262.02): C, 54.94; H, 3.84; N, 10.68; O, 6.10; and S, 24.44; found: C, 55.04; H, 3.74; N, 10.60; O, 6.17; and S, 24.53.

*7,8,9,10-Tetrahydrocyclohepta[4,5]thieno[2,3-d]thiazolo [3,2-a]pyrimidin-5(6H)-one (**3b**).* White solid; yield: 38%; mp: 145–147°C; IR (KBr, υ_{max}, cm^{-1}): 3130.08 (CH aromatic), 2917.76 (CH aliphatic), 1674.41 (C=O), and 1563.5, 1509.46 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.72 (*m*, 4H, H7, H9), 1.897 (*m*, 2H, H8), 2.838 (*t*, 2H, *J* = 5.4 Hz, H10), 3.365 (*t*, 2H, *J* = 4.8 Hz, H6), 6.855 (*d*, 1H, *J* = 4.8 Hz, H2), and 7.984 (*d*, 1H, *J* = 4.8 Hz, H3); ^{13}C NMR (δ, ppm, $CDCl_3$): 27.212, 27.672, 27.925, 29.895, 32.486 (C6-10), 109.494 (C2), 116.853 (C5a), 121.667 (C5a′), 135.634 (C3), 136.438 (C10a), 155.403 (C11a), 156.982 (C12a), and 162.317 (C5); and DART-TOF-MS (*m/z*): 277.05 $[M + H]^+$; anal. calcd. for $C_{13}H_{12}N_2OS_2$ (276.04): C, 56.50; H, 4.38; N, 10.14; O, 5.79; and S, 23.20; found: C, 56.43; H, 4.40; N, 10.18; O, 5.73; and S, 23.29.

*7,8-Dihydrocyclopenta[4,5]thieno[2,3-d]thiazolo[3,2-a] pyrimidin-5(6H)-imine (**3c**).* Dark green solid; yield: 22%; mp < 300°C; IR (KBr υ_{max}, cm^{-1}): 3241.38 (NH), 3073.4 (CH aromatic), 1643.81 (C=N), and 1590.95, 1509.8 (C=C aromatic); ^{1}H NMR (δ, ppm, DMSO-d_6): 2.469 (*m*, 2H, H7), 3.005 (*t*, 2H, H8), 3.15 (*t*, 2H, H6), 8.05 (*d*, 1H, *J* = 4.8 Hz, H2), 8.653 (*d*, 1H, *J* = 4.8 Hz, H3), and 9.172 (*s*, 1H, NH); and ^{13}C NMR (δ, ppm, DMSO-d_6): 27.664, 29.496, 29.971 (C6-8), 108.682 (C2), 118.210 (C5a), 122.395 (C5a′), 136.416 (C8a), 141.138 (C9a), 148.359 (C3), 157.121 (C5), and 168.972 (10a); and DART-TOF-MS (*m/z*): 248.03 $[M + H]^+$; anal. calcd. for $C_{11}H_9N_3S_2$ (247.02): C, 53.42; H, 3.67; N, 16.99; and S, 25.92; found: C, 53.47; H, 3.64; N, 17.05; and S, 25.89.

*6,7,8,9-Tetrahydro-5H-benzo[4,5]thieno[2,3-d]thiazolo [3,2-a]pyrimidin-5-imine (**3d**).* Yellow solid; yield: 88%;

mp < 300°C; IR (KBr, υ_{max}, cm^{-1}): 3281.42 (NH), 3080.16 (CH aromatic), 2929.63 (CH aliphatic), 1643.47 (C=N), and 1564.15, 1504.9 (C=C aromatic); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.835 (*s*, 4H, H7, H8), 2.824 (*s*, 2H, H6), 2.993 (*s*, 2H, H9), 8.002 (*d*, 1H, J = 4.8 Hz, H2), 8.619 (*d*, 1H, J = 4.8 Hz, H3), and 9.002 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 21.945, 22.144, 25.471, 25.931 (C6-9), 111.372 (C2), 118.003 (C5a), 122.319 (C5a′), 128.091 (C9a), 135.664 (C10a), 148.596 (C3), 157.573 (C5), and 164.303 (C11a); and DART-TOF-MS (*m/z*): 262.05 $[M + H]^+$; anal. calcd. for $C_{12}H_{11}N_3S_2$ (261.04): C, 55.15; H, 4.24; N, 16.08; and S, 24.53; found: C, 55.09; H, 4.31; N, 16.13; and S, 24.57.

*7,8,9,10-Tetrahydrocyclohepta[4,5]thieno[2,3-d]thiazolo [3,2-a]pyrimidin-5(6H)-imine (**3e**)*. Light brown solid; yield: 70%; mp < 300°C; IR (KBr, υ_{max}, cm^{-1}): 3270.42 (NH), 3053.25 (CH aromatic), 2906.04 (CH aliphatic), 1639.62 (C=N), and 1556.71, 1501.3 (C=C aromatic); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.714, 1.866, 2.953, 3.12 (*m*, 10H, H6-10), 8.02 (*d*, 1H, H2), 8.63 (*d*, 1H, H3), and 9.186 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 26.485, 26.914, 28.838, 28.93, 30.67 (C6-10), 112.192 (C2), 117.865 (C5a), 122.434 (C5a′), 133.319 (C10a), 139.765 (C11a), 148.941 (C3), 157.204 (C5), and 163.107 (C12a); and DART-TOF-MS (*m/z*): 276.07 $[M + H]^+$; anal. calcd. for $C_{13}H_{13}N_3S_2$ (275.06): C, 56.70; H, 4.76; N, 15.26; and S, 23.28; found: C, 56.74; H, 4.72; N, 15.34; and S, 23.33.

*2.2.2. Synthetic Procedure for Compounds (**4a–e**, **5**).* Compounds **2b–f** (1.7 mmol) were refluxed in bromoalkanoyl chloride for 2–3 h. Then, the mixture was left at room temperature until the product precipitated. The precipitate was filtered, washed with absolute ethanol, dried, and recrystallized from a mixture of absolute ethanol and methanol.

*Ethyl-2-(5-bromopentanamido)-5,6-dihydro-4H-cyclopenta [b]thiophene-3-carboxylate (**4a**)*. Greenish white solid; yield: 25%; mp: 57–59°C; IR (KBr, υ_{max}, cm^{-1}): 3271.77 (NH), 2944.81 (CH aliphatic), 1669.36 (C=O), and 1558.46, 1520.71 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.353 (*t*, 3H, J = 6.6 Hz, -$CH_2\underline{CH_3}$), 1.916 (*m*, 4H, H3′-4′), 2.356 (*m*, 2H, J = 6.6 Hz, H5), 2.491 (*t*, 2H, J = 6.6 Hz, H2′), 2.82 (*t*, 2H, H6), 2.867 (*t*, 2H, H4), 3.419 (*t*, 2H, J = 5.4 Hz, H5′), 4.29 (*q*, 2H, J = 6.6 Hz, -$C\underline{H_2}CH_3$), and 11.004 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, $CDCl_3$): 14.271 (-CH_2CH_3), 22.481, 23.731, 27.908, 28.828, 30.262, 31.940, 32.929, 35.589 (C4-6, C2′-5′), 60.441 (-$\underline{C}H_2CH_3$), 108.083 (C3), 132.169 (C6a), 141.214 (C3a), 151.341 (C=O ester), 166.143 (C=O amide), and 169.11 (C2); and DART-TOF-MS (*m/z*): 374.04 $[M + H]^+$; anal. calcd. for $C_{15}H_{20}BrNO_3S$ (373.03): C, 48.13; H, 5.39; Br, 21.35; N, 3.74; O, 12.82; and S, 8.57; found: C, 48.18; H, 5.24; Br, 21.41; N, 3.69; O, 12.77; and S, 8.52.

*5-Bromo-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl)pentanamide (**4b**)*. White solid; yield: 74%; mp: 149–150°C; IR (KBr, υ_{max}, cm^{-1}): 3468.26 (NH), 2935.12 (CH aliphatic), 2214.8 (CN), 1699.82 (C=O), and 1548.87, 1455.74 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.818–1.967 (*m*, 8H, H5-6, H3′-4′) 2.569, 2.614 (*m*, 4H, H4, H7), 2.533 (*t*, 2H, H2′), 3.433 (*t*, 2H, H5′), and 9.277 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, $CDCl_3$): 22.115, 23.065, 23.74, 23.885, 23.954, 31.942, 32.946, 34.794 (C4-7, C2′-5′), 92.316 (C3), 114.814 (CN), 128.083 (C7a), 130.689 (C3a), 147.507 (C2), and 169.829 (C=O amide); and DART-TOF-MS (*m/z*): 341.03 $[M + H]^+$; anal. calcd. for $C_{14}H_{17}BrN_2OS$ (340.02): C, 49.27; H, 5.02; Br, 23.41; N, 8.21; O, 4.69; and S, 9.39; found: C, 49.32; H, 4.98; Br, 23.49; N, 8.17; O, 4.73; and S, 9.31.

*5-Bromo-N-(3-cyano-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophen-2-yl)pentanamide (**4c**)*. Beige solid; yield: 82%; mp: 127–129°C; IR (KBr, υ_{max}, cm^{-1}): 3486.48 (NH), 2924.92 (CH aliphatic), 2213.55 (CN), 1696.13 (C=O), and 1544.89, 1441.07 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.656 (*m*, 4H, H5, H7), 1.85–1.951 (*m*, H2′-4′), 2.507 (*m*, 2H, H6), 2.697 (*s*, 4H, H4, H8), 3.431, 3.567 (*m*, 2H, H5′), and 8.575 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, $CDCl_3$): 22.483, 23.725, 27.32, 27.994, 29.044, 31.758, 31.888, 32.003, 34.947 (C4-8, C2′-5′), 95.106 (C3), 115.159 (CN), 131.77 (C8a), 135.465 (C3a), 145.031 (C2), and 169.623 (C=O amide); and DART-TOF-MS (*m/z*): 355.05 $[M + H]^+$; anal. calcd. for $C_{15}H_{19}BrN_2OS$ (354.04): C, 50.71; H, 5.39; Br, 22.49; N, 7.88; O, 4.50; and S, 9.02; found: C, 50.78; H, 5.34; Br, 22.41; N, 7.93; O, 4.47; and S, 8.96.

*Ethyl-2-(6-bromohexanamido)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylate (**4d**)*. White solid; yield: 43%; mp: 66–67°C; IR (KBr, υ_{max}, cm^{-1}): 3360.95 (NH), 2915.27 (CH aliphatic), 1675.80 (C=O), and 1529.22 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.379 (*t*, 3H, J = 7.2 Hz, -$CH_2C\underline{H_3}$), 1.508 (*m*, 2H, H4′), 1.594, 1.638 (4H, H5, H7), 1.756 (*m*, 2H, H3′), 1.826 (*s*, 2H, H6), 1.888 (*m*, 2H, H5′), 2.456 (*t*, 2H, J = 7.2 Hz, H2′), 2.699 (*m*, 2H, H8), 3.015 (*m*, 2H, H4), 3.396 (*t*, 2H, J = 6.6 Hz, H6′), 4.33 (*q*, 2H, J = 7.2 Hz, -$C\underline{H_2}CH_3$), and 11.2 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, $CDCl_3$): 14.25 (-$CH_2\underline{C}H_3$), 24.442, 26.936, 27.688, 27.795, 28.247, 28.561, 32.21, 32.417, 33.444, 36.564 (C4-8, C2′-6′), 60.649 (-$\underline{C}H_2CH_3$), 112.668 (C3), 130.843 (C8a), 136.270 (C3a), 145.484 (C=O ester), 166.748 (C=O amide), and 169.554 (C2); and DART-TOF-MS (*m/z*): 416.09 $[M + H]^+$; anal. calcd. for $C_{18}H_{26}BrNO_3S$ (415.08): C, 51.92; H, 6.29; Br, 19.19; N, 3.36; O, 11.53; and S, 7.70; found: C, 51.88; H, 6.34; Br, 19.25; N, 3.31; O, 11.47; and S, 7.79.

*6-Bromo-N-(3-cyano-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophen-2-yl)hexan-amide(**4e**)*. Brown solid; yield: 69%; mp: 104–106°C; IR (KBr, υ_{max}, cm^{-1}): 3420.51 (NH), 2925.32 (CH aliphatic), 2217.32 (CN), 1688.82 (C=O), and 1552.66, 1439.5 (C=C aromatic); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.529 (*m*, 2H, H4′), 1.66 (*m*, 4H, H5, H7), 1.765 (*m*, 2H, H3′), 1.85 (*m*, 2H, H6), 1.899 (*m*, 2H, H5′), 2.496 (*t*, 2H, J = 7.2 Hz, H2′), 2.694 (*m*, 4H, H4, H8), 3.409 (*t*, 2H, J = 6.6 Hz, H6′), and 8.91 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, $CDCl_3$): 24.322, 27.327, 27.665, 27.994, 29.044, 29.067, 31.996, 32.364, 33.406, 35.706 (C4-8, C2′-6′), 95.075 (C3), 115.151 (CN), 131.716 (C8a), 135.411 (C3a), 145.07 (C2), and 169.921 (C=O amide); and DART-TOF-MS (*m/z*): 369.07 $[M + H]^+$; anal. calcd. for $C_{16}H_{21}BrN_2OS$ (368.06): C, 52.03; H, 5.73; Br, 21.64; N, 7.59; O, 4.33; and S, 8.68; found: C, 52.08f H, 5.64; Br, 21.69; N, 7.51; O, 4.37; and S, 8.62.

*2-(5-Bromopentyl)-5,6,7,8-tetrahydro-4H-benzo[4,5]thieno [2,3-d][1,3]oxazin-4-imine (**5**)*. White solid; yield: 40%; mp: 174–175°C; IR (KBr, υ_{max}, cm^{-1}): 2936.82 (CH

aliphatic), 1664.9 (C=N), and 1588.12 (C=C); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.376 (*m*, 2H, H3′), 1.641–1.816 (*m*, 8H, H2′, H4′, H7-8), 2.553 (*t*, 2H, J = 6.6 Hz, H1′), 2.686 (*s*, 2H, H6), 2.821 (*s*, 2H, H6), 3.508 (*t*, 2H, J = 6.6 Hz, H5), and 12.177 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 22.246, 22.966, 24.821, 25.726, 26.4, 27.343, 32.264, 34.058, 35.469 (C6-9, C1′-5′), 120.778 (C4a), 130.965 (C4a′), 131.395 (C9a), 157.787 (C10a), 159.013 (C4), and 163.559 (C2); and DART-TOF-MS (*m/z*): 355.05 $[M + H]^+$; anal. calcd. for $C_{15}H_{19}BrN_2OS$ (354.04): C, 50.71; H, 5.39; Br, 22.49; N, 7.88; O, 4.50; and S, 9.02; found: C, 50.76; H, 5.32; Br, 22.52; N, 7.85; O, 4.53; and S, 8.96.

*2.2.3. General Synthetic Procedure for 1-(3-Cyano-substituted [b]thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (**6a–c**).* A mixture of the appropriate compound **2d–f** (1.3 mmol) with 1 equivalent of 4-(trifluoromethyl)phenyl isothiocyanate in absolute ethanol was stirred at room temperature for 2–7 h. The precipitate was filtered, washed with absolute ethanol, and dried.

*1-(3-Cyano-5,6-dihydro-4H-cyclopenta[b]thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (**6a**).* Light brown solid; yield: 31%; mp: 172–174°C; IR (KBr, υ_{max}, cm^{-1}): 3327.76, 3234.11 (NH), 2212.49 (CN), and 1589.8, 1560.47 (C=C); ^{1}H NMR (δ, ppm, DMSO-d_6): 2.323 (*s*, 2H, H5), 2.72 (*s*, 2H, H6), 2.814 (*s*, 2H, H4), 7.701 (*s*, 2H, H2′, H6′), 7.818 (*s*, 2H, H3′, H5′), 10.71 (*s*, 1H, NH), and 10.95 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 27.786, 28.039, 29.649 (C4-5), 115.036 (CN), 123.139 (C3′, C5′), 126.236 (C2′, C6′), and 130.613 (C3a); and DART-TOF-MS (*m/z*): 368.05 $[M + H]^+$; anal. calcd. for $C_{16}H_{12}F_3N_3S_2$ (367.04): C, 52.31; H, 3.29; F, 15.51; N, 11.44; and S, 17.45; found: C, 52.27; H, 3.35; F, 15.55; N, 11.38; and S, 17.40.

*1-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (**6b**).* Light beige solid; yield: 49%; mp: 187–189°C; IR (KBr, υ_{max}, cm^{-1}): 3328.78, 3235.86 (NH), 2210.19 (CN), and 1590.92, 1560.13 (C=C); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.74 (*s*, 4H, H5-6), 2.498 (*m*, 2H, H7), 2.585 (*s*, 2H, H4), 7.715 (*d*, 2H, J = 7.8 Hz, H2′, H6′), 7.838 (*d*, 2H, J = 7.8 Hz, H3′, H5′), 10.765 (*s*, 1H, NH), and 11.016 (*s*, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 22.146, 23.05, 23.809, 23.848 (C4-7), 96.041 (C3), 114.791 (CN), 123.07 (C3′, C5′), 123.775 (CF_3), 125.584 (C4′), 126.297 (C2′, C6′), 128.581 (C3a), 130.988 (C7a), 142.862 (C1′), 148.895 (C2), and 176.728 (C=S); and DART-TOF-MS (*m/z*): 382.07 $[M + H]^+$ anal. calcd. for $C_{17}H_{14}F_3N_3S_2$ (381.06): C, 53.53; H, 3.70; F, 14.94; N, 11.02; and S, 16.81; found: C, 53.57; H, 3.64; F, 15.0; N, 11.06; and S, 16.75.

*1-(3-Cyano-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl)-3-(4-(trifluoro-methyl)phenyl)thiourea (**6c**).* Dark beige solid; yield: 32%; mp: 169–171°C; IR (KBr, υ_{max}, cm^{-1}): 3326.54 (NH), 2211.97 (CN), and 1582.92, 1554.87 (C=C); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.572 (*s*, 4H, H5, H7), 1.781 (*s*, 2H, H6), 2.633–2.674 (*m*, 4H, H4, H8), 7.705 (*d*, 2H, J = 8.4 Hz, H2′, H6′), 7.828 (*d*, 2H, J = 8.4 Hz, H3′, H5′), 10.777 (*s*, 1H, NH), and 10.937 (*s*, 1H, NH);^{13}C NMR (δ, ppm, DMSO-d_6): 27.334, 28.07, 28.783, 31.78 (C4-8), 98.241 (C3), 115.266 (CN), 122.955 (C3′, C5′), 123.77 (CF_3), 125.577 (C4′), 126.274 (C2′, C6′), 131.947(C3a), 135.634 (C8a), 142.855 (C1′), 146.787 (C2), and 176.507 (C=S); DART-TOF-MS (*m/z*): 396.08 $[M + H]^+$; anal. calcd. for $C_{18}H_{16}F_3N_3S_2$ (395.07): C, 54.67; H, 4.08; F, 14.41; N, 10.63; and S, 16.21; found: C, 54.77; H, 3.99; F, 14.46; N, 10.68; and S, 16.16.

*2.2.4. General Synthetic Procedure for Compounds (**7a–f**).* Few drops of sulfuric acid were added to a mixture of the appropriate lead compound **2d–f** (5.6 mmol) and 1 equivalent of 4-(trifluoromethyl)benzaldehyde or 4-(2-pyridyl) benzaldehyde in absolute ethanol. Precipitation occurred once sulfuric acid was added. The precipitate was filtered, washed with absolute ethanol, and dried.

*2-((4-(Trifluoromethyl)benzylidene)amino)-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (**7a**).* Dark brown solid; yield: 41%; mp: 150–152°C; IR (KBr, υ_{max}, cm^{-1}): 2219.12 (CN), 1678.47 (C=N), and 1567.51, 1536.64 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 2.444 (*m*, 2H, H5), 2.873 (*t*, 2H, H6), 2.946 (*t*, 2H, H4), 7.704 (*d*, 2H, J = 7.8 Hz, H3′, H5′), 8.033 (*d*, 2H, J = 7.8 Hz, H2′, H6′), and 8.468 (*s*, 1H, N=CH); ^{13}C NMR (δ, ppm, $CDCl_3$): 27.379, 28.169, 30.239 (C4-6), 103.913 (C3), 114.492 (CN), 124.611 (CF_3), 125.814 (C3′, C5′), 129.44 (C2′, C6′), 133.441 (C4′), 138.087 (C3a), 139.007 (C1′), 145.108 (C6a), 155.649 (C2), and 163.744 (N=CH); and DART-TOF-MS (*m/z*): 321.07 $[M + H]^+$; anal. calcd. for $C_{16}H_{11}F_3N_2S$ (320.06): C, 59.99; H, 3.46; F, 17.79; N, 8.75; and S, 10.01; found: C, 60.07; H, 3.39; F, 17.84; N, 8.80; and S, 9.97.

*2-((4-(Trifluoromethyl)benzylidene)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**7b**).* Yellow solid; yield: 78%; mp: 146–147°C; IR (KBr, υ_{max}, cm^{-1}): 2216.15 (CN), 1659.53 (C=N), and 1563.09, 1514.72 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.861 (*m*, 4H, H5, H6), 2.664 (*s*, 2H, H7), 2.711 (*s*, 2H, H4), 7.696 (*d*, 2H, J = 7.8 Hz, H3′, H5′), 8.026 (*d*, 2H, J = 7.8 Hz, H2′, H6′), and 8.422 (*s*, 1H, N=CH); ^{13}C NMR (δ, ppm, $CDCl_3$): 21.914, 22.987, 24.282, 25.271 (C4-7), 108.39 (C3), 114.201 (CN), 124.618 (CF_3), 125.799 (C3′, C5′), 129.448 (C2′, C6′), 133.426 (C4′), 133.832 (C3a), 135.572 (C1′), 138.102 (C7a), 156.73 (C2), and 158.569 (N=CH); and DART-TOF-MS (*m/z*): 335.09 $[M + H]^+$; anal. calcd. for $C_{17}H_{13}F_3N_2S$ (334.08): C, 61.07; H, 3.92; F, 17.05; N, 8.38; and S, 9.59; found: C, 61.12; H, 3.86; F, 16.98; N, 8.42; and S, 9.55.

*2-((4-(Trifluoromethyl)benzylidene)amino)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile (**7c**).* Yellow solid; yield: 99%; mp: 113–114°C; IR (KBr, υ_{max}, cm^{-1}): 2221.48 (CN), 1684.98 (C=N), and 1547.17, 1517.48 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.7 (*m*, 4H, H5, H7), 1.882 (*s*, 2H, H6), 2.804 (*t*, 4H, H4, H8), 7.7 (*d*, 2H, J = 7.8 Hz, H3′, H5′), 8.026 (*d*, 2H, J = 7.8 Hz, H2′, H6′), and 8.438 (*s*, 1H, N=CH); ^{13}C NMR (δ, ppm, $CDCl_3$): 27.073, 27.755, 29.142, 30.691, 31.956 (C4-8), 110.605 (C3), 114.729 (CN), 122.824 (CF_3), 125.776 (C3′, C5′), 129.356 (C2′, C6′), 133.150 (C4′), 137.558 (C3a), 138.186 (C1′), 140.624 (C8a), 156.538 (C2), and 156.576 (N=CH); and DART-TOF-MS (*m/z*): 349.1 $[M + H]^+$; anal. calcd. for $C_{18}H_{15}F_3N_2S$ (348.09): C,

62.06; H, 4.34; F, 16.36; N, 8.04; and S, 9.20; found: C, 62.12; H, 4.30; F, 16.45; N, 8.0; and S, 9.25.

*2-((4-(Pyridin-2-yl)benzylidene)amino)-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (**7d**)*. Yellow solid; yield: 29%; mp: 191–193°C; IR (KBr, υ_{max}, cm^{-1}): 2219.27 (CN), and 1581.62, 1548.56 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 2.433 (*m*, 2H, $J = 7.2$ Hz, H5), 2.869 (*t*, 2H, $J = 7.2$ Hz, H6), 2.934 (*t*, 2H, $J = 7.2$ Hz, H4), 7.273 (*t*, 1H, H4″), 7.794 (*m*, 2H, $J = 7.2$ Hz, H5″, H6″), 8.032 (*d*, 2H, $J = 7.8$ Hz, H2′, H6′), 8.106 (*d*, 2H, $J = 7.8$ Hz, H3′, H5′), 8.488 (*s*, 1H, N=CH), and 8.719 (*d*, 1H, H3″); ^{13}C NMR (δ, ppm, $CDCl_3$): 27.356, 28.215, 30.223 (C4-6), 102.779 (C3), 114.814 (CN), 120.946 (C6″), 122.794 (C4″), 127.294, 129.869 (C2′-3′, C5′-6′), 135.404 (C3a), 136.906 (C1′), 137.887 (C5″), 142.809 (C6a), 144.787 (C4′), 149.884 (C3″), 156.185 (C1″), 157.236 (C2), and 164.986 (N=CH); and DART-TOF-MS (*m/z*): 330.11 $[M + H]^+$; anal. calcd. for $C_{20}H_{15}N_3S$ (329.10): C, 72.92; H, 4.59; N, 12.76; and S, 9.73; found: C, 72.88; H, 4.55; N, 12.81; and S, 9.69.

*2-((4-(Pyridin-2-yl)benzylidene)amino)-4,5,6,7-tetrahydro benzo[b]thiophene-3-carbonitrile (**7e**)*. Yellow solid; yield: 83%; mp: 191–193°C; IR (KBr, υ_{max}, cm^{-1}): 2214.28 (CN), and 1582.55, 1552.3 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.853 (*m*, 4H, H5-6), 2.68 (*d*, 4H, H4, H7), 7.272 (*m*, 1H, H4″), 7.788 (*s*, 2H, H5″, H6″), 8.019 (*d*, 2H, $J = 7.8$ Hz, H2′, H6′), 8.094 (*d*, 2H, $J = 7.8$ Hz, H3′, H5′), 8.433 (*s*, 1H, N=CH), and 8.719 (*s*, 1H, H3″); ^{13}C NMR (δ, ppm, $CDCl_3$): 21.984, 23.05, 24.299, 25.25 (C4-5), 107.256 (C3), 114.538 (CN), 120.969 (C6″), 122.817 (C4″), 127.278 (C3′, C5′), 129.869 (C2′, C6′), 132.797 (C3a), 135.235 (C1′), 135.434 (C5″), 136.96 (C7a), 142.739 (C4′), 149.853 (C3″), 156.147 (C1″), 158.27 (C2), and 159.749 (N=CH); and DART-TOF-MS (*m/z*): 344.12 $[M + H]^+$; anal. calcd. for $C_{21}H_{17}N_3S$ (343.11): C, 73.44; H, 4.99; N, 12.24; and S, 9.33; found: C, 73.48; H, 4.94; N, 12.31; and S, 9.27.

*2-((4-(Pyridin-2-yl)benzylidene)amino)-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-3-carbonitrile (**7f**)*. Yellow solid; yield: 86%; mp: 199–200°C; IR (KBr, υ_{max}, cm^{-1}): 2218.75 (CN), and 1582.43, 1546.89 (C=C); ^{1}H NMR (δ, ppm, $CDCl_3$): 1.703 (*m*, 4H, H5, H7), 1.88 (*s*, 2H, H6), 2.801 (*m*, 4H, H4, H8), 7.275 (*s*, 1H, H4″), 7.795 (*m*, 2H, H5″, H6″), 8.026 (*d*, 2H, $J = 7.8$ Hz, H2′, H6′), 8.102 (*d*, 2H, $J = 7.8$ Hz, H3′, H5′), 8.463 (*s*, 1H, N=CH), and 8.722 (*s*, 1H, H3″); ^{13}C NMR (δ, ppm, $CDCl_3$): 27.126, 27.809, 29.15, 30.653, 31.994 (C4-8), 109.532 (C3), 115.036 (CN), 120.946 (C6″), 122.771 (C4″), 127.286 (C3′, C5′), 129.777 (C2′, C6′), 135.519 (C3a), 136.462 (C1′), 136.922 (C5″), 140.279 (C8a), 142.701 (C4′), 149.861 (C3″), 156.224 (C1″), 157.726 (C2), and 158.155 (N=CH); and DART-TOF-MS (*m/z*): 358.14 $[M + H]^+$; anal. calcd. for $C_{22}H_{19}N_3S$ (357.13): C, 73.92; H, 5.36; N, 11.75; and S, 8.97; found: C, 73.97; H, 5.29; N, 11.81; and S, 9.02.

2.3. X-Ray Crystallographic Analysis. Compounds **4c** and **7e** were obtained as single crystals by slow evaporation of the ethanol solution of the pure compounds at room temperature. Crystallographic data were collected using a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo Kα radiation, $\lambda = 0.71073$, and Cu Kα radiation, $\lambda = 1.54178$ Å at 293 (2) K. Cell refinement and data reduction were carried out using Bruker SAINT. SheLXT was used to determine the structure [24, 25]. The final refinement was carried out by the full-matrix least-squares technique with anisotropic thermal data for -non-hydrogen atoms on F-CCDC 1823351 and 1534088 that contain the supplementary crystallographic data for these compounds obtained free of charge from the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/data_request/cif).

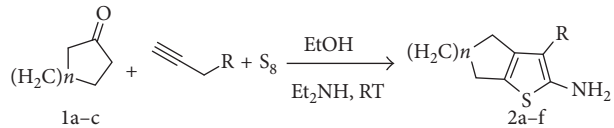
2.4. Biology

2.4.1. Evaluation of Antimicrobial Activity. All selected organisms (0.5 McFarland standards) were thoroughly mixed with sterilized Mueller–Hinton agar (MHA). This suspension (25 mL) was placed into Petri dishes (90 mm diameter) and left to cool and solidify by placing the Petri dishes on a cool horizontal surface. A 10 mm diameter well was holed on both sides of the agar plate by using a sterilized hollow cylinder as a template. The formulations and control antibiotics (1 mg/mL) were placed into each well (50 μL) to permit diffusion. All plates were incubated at 37 ± 0.5°C for 24 h in aerobic conditions; the test was performed in triplicate. The antimicrobial activities of the selected formulations and control antibiotics against the tested microorganisms were compared. The diameter of the inhibition zone was measured with a gauge and expressed in mm (mean ± standard deviation (SD)).

2.4.2. Evaluation of Anti-Inflammatory Activity. Fresh whole human blood was collected and mixed with equal volumes of sterilized Alsever's solution (2% dextrose, 0.8% sodium citrate, 0.05% citric acid, 0.42% sodium chloride, and 100 mL of distilled water). This blood solution was centrifuged at 3,000 rpm for 10 min and then washed three times with an equal volume of normal saline. The volume of blood was measured, and it was reconstituted with normal saline to prepare 10% *v/v* suspension. The reaction mixture consisted of 1 mL of the test sample in normal saline at different concentrations: 0.5 mL of 10% human red blood cell (HRBC) suspension, 1mL of 0.2 M phosphate buffer, and 1 mL of hypotonic saline. They were incubated at 37°C for 30 min and centrifuged at 3,000 rpm for 30 min. Hemoglobin content in the supernatant was determined spectrophotometrically at 560 nm. Each experiment was performed in triplicate. Diclofenac sodium was used as a standard, and distilled water was used as a control. The blood control represented 100% lysis or zero percent stability.

3. Results and Discussion

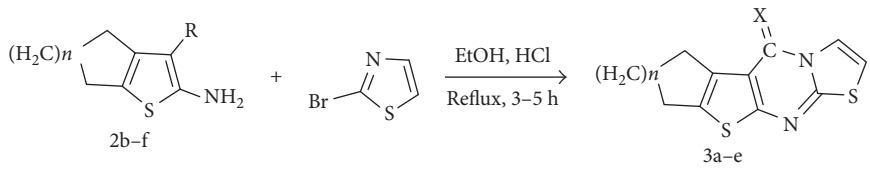
3.1. Chemistry. Using the Gewald method for thiophene synthesis, we synthesized the lead compounds (**2a–f**) (Scheme 1) [26, 27].



a n = 1
b n = 2
c n = 3

a n = 1, R = –COOEt
b n = 2, R = –COOEt
c n = 3, R = –COOEt
d n = 1, R = –CN
e n = 2, R = –CN
f n = 3, R = –CN

Scheme 1: Gewald thiophene synthesis.



b n = 2, R = –COOEt
c n = 3, R = –COOEt
d n = 1, R = CN
e n = 2, R = CN
f n = 3, R = CN

a n = 2, X = O
b n = 3, X = O
c n = 1, X = NH
d n = 2, X = NH
e n = 3, X = NH

Scheme 2: Synthesis of thieno[2,3-(d)]thiazolo[3,2-(a)]pyrimidine derivatives (**3a–e**).

A mixture of the appropriate compound (**2b–f**), 2-bromothiazole, and few drops of hydrochloric acid in ethanol was refluxed for 3–5 h to produce thieno[2,3-*d*]thiazolo [3,2-*a*]pyrimidine derivatives (Scheme 2).

This reaction involves nucleophilic substitution in bromothiazole followed by nucleophilic substitution on the ester group to form the pyrimidinone ring (compounds **3a–b**). However, for compounds **3c–e**, nucleophilic substitution was followed by nucleophilic addition of a cyanide group to the thiazole nitrogen to form the pyrimidinimine ring.

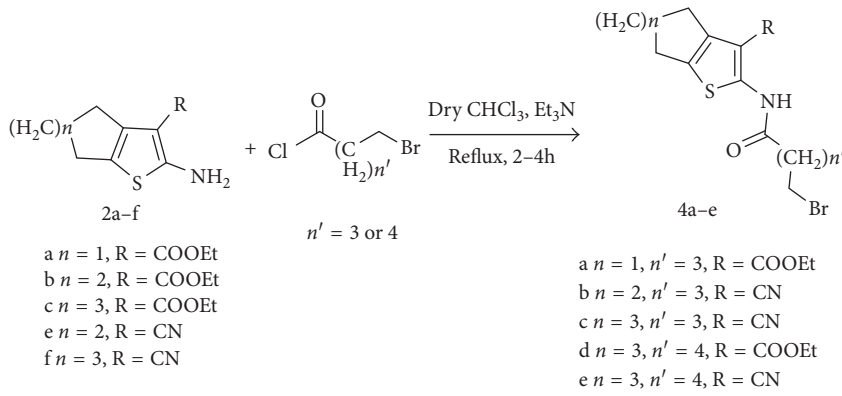
IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data of the polycyclic compound **3a** and new compounds **3b–e** were consistent with the assigned structures. The IR spectrum of compound **3b** showed an absorption band at 1674.41 cm^{-1} for the carbonyl group, whereas there was no amino group absorption band. The ^{1}H NMR spectrum showed the presence of the cycloheptenyl protons and appearance of new signals: two doublet signals at δ = 6.855 and 7.984 ppm (each integrates for one proton corresponding to the two protons of the thiazole ring) with coupling constant (J) = 4.8 Hz, whereas there was no signal for the ethyl group linked to the ester group. In ^{13}C NMR, the three carbons of the thiazole group appeared at δ = 109.494, 121.667, and 156.982 ppm, carbonyl peak appeared at δ = 162.317 ppm, and no peaks for the ethyl group. Finally, the direct analysis in real-time/time-of-flight mass spectrometry (DART-TOF-MS) spectrum showed a molecular ion peak $[M + H]^+$ at m/z = 277.05.

The lead compounds (**2b–f**) were refluxed in bromoalkanoyl chloride derivatives (Scheme 3) to produce compounds (**4a–e**) by nucleophilic substitution reaction.

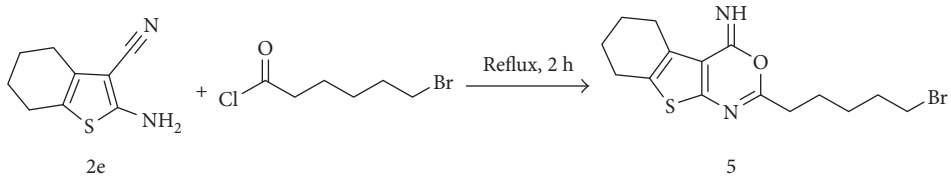
However, the nucleophilic substitution reaction between compound **2e** and 6-bromohexanoyl chloride was followed by nucleophilic addition of a cyanide group to the carbonyl oxygen to form the oxazinimine ring of the novel compound **5** (Scheme 4).

The IR data of compound **4d** showed the appearance of an NH absorption band at 3360.95 cm^{-1} and another absorption band with two heads at 1675.80 cm^{-1}, which represents the two carbonyl groups. In ^{1}H NMR, five new signals appeared: multiplet at δ = 1.508, 1.756, and 1.888 ppm and triplet at δ = 2.456 and 3.396 ppm (each signal integrates for two protons corresponding to the protons of the side chain). In addition, one proton singlet signal for NH appeared at δ = 11.2 ppm. The ^{13}C NMR spectrum showed the appearance of the five carbons of the side chain in the aliphatic range; besides, it showed signals for the cycloheptenyl carbons in the range of δ = 24.442–36.564 ppm and a peak for the amide group at δ = 166.748 ppm. Finally, the DART-TOF-MS spectrum showed a molecular ion peak $[M + H]^+$ at m/z = 416.09.

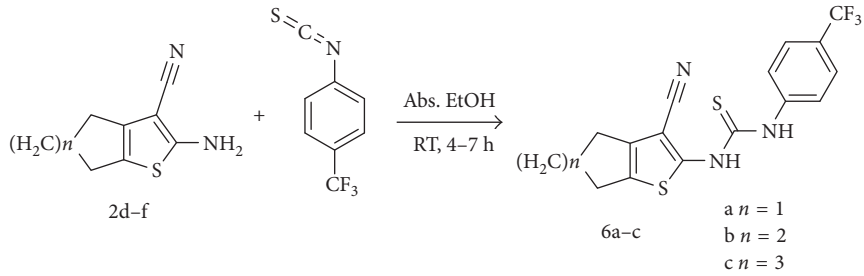
For compound **5**, the disappearance of the cyanide absorption band in the IR spectrum, appearance of one proton signal for NH at δ = 12.177 ppm in the ^{1}H NMR spectrum, and appearance of carbon peaks at δ = 159.013 and 163.559 ppm for C4 and C2, respectively, in the ^{13}C NMR spectrum proved the formation of the oxazinimine ring. The six protons of the side chain appeared in the ^{1}H NMR spectrum as multiplet signals at δ = 1.376 and 1.641–1.816 ppm for H2–H4′ and two triplet signals at δ = 2.533 and 3.508 ppm for H1′ and H5′, respectively (each signal integrates for two protons). Moreover, the ^{13}C NMR spectrum showed the five carbons of the side



Scheme 3: Synthesis of compounds **4a–e**.



Scheme 4: Synthesis of thieno[2,3-(d)][1,3]oxazin-4-imine derivative (**5**).



Scheme 5: Synthesis of thiophene-thiourea derivatives (**6a–c**).

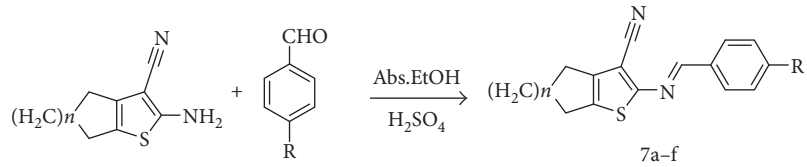
chain in the aliphatic range. Finally, the molecular weight was confirmed by the appearance of a molecular ion peak $[M+H]^+$ at $m/z = 355.05$ in the DART-TOF-MS spectrum.

A mixture of the appropriate lead compound (**2d–f**) and 4-(trifluoromethyl phenyl) isothiocyanate in absolute ethanol was stirred at 25°C for 2–7 h. The new thiophene-thiourea derivatives (**6a–c**) were obtained by nucleophilic addition (Scheme 5).

Structures of compounds (**6a–c**) were confirmed by the presence of a cyanide group and appearance of (4-(trifluoromethyl)phenyl)thiourea bands and peaks in the IR, ^{1}H NMR, and ^{13}C NMR spectra. Herein, for compound **6b**, the IR spectrum showed two absorption bands for the two NH groups at 3328.78 and 3235.86 cm^{-1} and an absorption band for cyanide at 2210.19 cm^{-1}. The ^{1}H NMR spectrum showed a doublet signal (2 H) with $J = 7.8$ Hz at $\delta = 7.715$ ppm for H2′ and H6′, doublet signal (2 H) with $J = 7.8$ Hz at $\delta = 7.838$ ppm for H3′ and H5′, and two singlet signals for NH at $\delta = 10.765$ and 11.016 ppm (each integrates for one proton). The ^{13}C NMR spectrum showed a peak for cyanide at $\delta = 114.791$ ppm; additionally, the phenyl ring carbons appeared as follows: C3′ and C5′ at $\delta = 123.07$ ppm, C2′ and C6′ at $\delta = 126.297$ ppm, C4′ at $\delta = 130.988$ ppm, and C1′ at $\delta = 142.862$ ppm. CF_3 appeared at $\delta = 123.77$ ppm, whereas the thionyl group appeared at $\delta = 176.728$ ppm. Finally, the molecular weight was confirmed by the appearance of a molecular ion peak $[M+H]^+$ at $m/z = 382.07$ in the DART-TOF-MS spectrum.

Addition of few drops of sulfuric acid to a mixture of the appropriate lead compound (**2d–f**) and 4-(trifluoromethyl) benzaldehyde or 4-(2-pyridyl) benzaldehyde in absolute ethanol resulted in instant precipitation of the product (Scheme 6).

All structures of the novel synthesized compounds (**7a–f**) were confirmed by the existence of a cyanide group, disappearance of NH_2, and appearance of 4-(trifluoromethyl) benzylidene or 4-(pyridin-2-yl)benzylidene bands and peaks in the IR, ^{1}H NMR, and ^{13}C NMR spectra. For instance, compound **7d** showed a cyanide absorption band at



Scheme 6: Synthesis of thiophene-3-carbonitrile derivatives (**7a–f**).

Table 1: Experimental detail of the crystalline structures of **4c** and **7e**.

Crystal data	**4c**	**7e**
Chemical formula	$C_{15}H_{19}BrN_2OS$	$C_{21}H_{17}N_3S$
Molecular weight	355.29	343.44
Crystal system, space group	Triclinic, $P-1$	Triclinic, $P-1$
Temperature (K)	293	293
a, b, c (Å)	5.7305 (7), 9.0388 (13), 15.825 (2)	6.6424 (6), 11.5386 (10), 11.5868 (10)
α, β, γ (°)	97.214 (5), 97.557 (5), 90.726 (5)	98.088 (3), 93.063 (3), 98.051 (3)
V (Å^3)	805.76 (18)	868.13 (13)
Z	2	2
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	2.68	0.19
Crystal size (mm)	$0.55 \times 0.42 \times 0.04$	$0.4 \times 0.29 \times 0.1$
Data collection		
Diffractometer	Bruker APEX-II D8 venture diffractometer	Bruker APEX-II D8 venture diffractometer
Absorption correction	Multiscan SADABS Bruker 2014	Multiscan SADABS Bruker 2014
T_{min}, T_{max}	0.893, 0.921	0.927, 0.982
Number of measured, independent, and observed [$I > 2\sigma(I)$] reflections	16032, 3700, and 1871	33436, 3412, and 2377
R_{int}	0.152	0.103
Refinement		
$R[F^2 > 2\sigma(F^2)]$, wR(F^2), S	0.114, 0.341, 1.66	0.066, 0.201, 1.08
Number of reflections	3700	3412
Number of parameters	176	226
Number of restraints	0	1
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.37, −1.74	0.34, −0.33
CCDC number	1823351	1534088

2219.27 cm^{-1} and disappearance of the NH_2 bands in the IR spectrum. The ^{1}H NMR spectrum showed signals of the pyridyl ring protons as follows: a triplet signal (1 H) at $\delta = 7.273$ ppm for H4″, multiplet signal (2 H) at $\delta = 7.794$ ppm for H5″ and H6″, and doublet signal at $\delta = 8.719$ ppm for H3″. In addition, the four protons of the benzene ring appeared as two doublet signals (each integrates for two protons) with $J = 7.2$ Hz at $\delta = 8.032$ and 8.106 ppm. Moreover, an N=CH singlet signal (1 H) appeared at $\delta = 8.488$ ppm. ^{13}C NMR showed a cyanide peak ($\delta =$ 114.814 ppm), pyridyl ring peaks (C6″ at $\delta = 120.946$ ppm, C4″ peak at $\delta = 122.794$ ppm, C5″ peak at $\delta = 137.887$ ppm, C3″ peak at $\delta = 149.884$ ppm, and C1″ peak at $\delta =$ 156.185 ppm), benzene ring peaks (C2′ and C3′ at $\delta = 127.294$, C5′ and C6′ at 129.869 ppm, C1′ at $\delta = 136.906$ ppm, and C4′ at $\delta = 144.787$ ppm), and N=CH peak at $\delta = 164.986$ ppm. DART-TOF-MS confirmed the molecular weight of the expected structure, as evidenced by the appearance of a molecular ion peak $[M + H]^+$ at $m/z = 330.11$.

3.2. X-Ray Crystallography. The structures of three of the synthesized compounds (**4c**, **7e**) were examined by X-ray crystallography. The crystallographic data and refinement information are summarized in Table 1. As shown in Figure 2, the asymmetric units contained one independent molecule.

3.3. Biology

3.3.1. Evaluation of Antimicrobial Activity. An *in vitro* antimicrobial study was performed using the agar diffusion method to evaluate the ability of the synthesized compounds to inhibit microbial growth, as previously described by

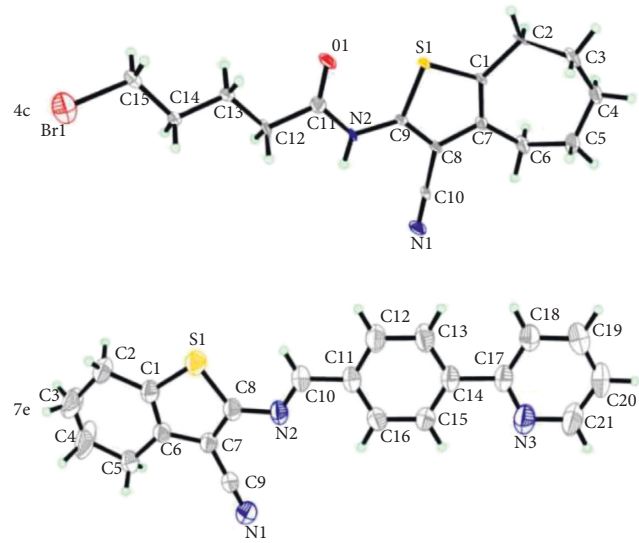


Figure 2: ORTEP diagrams of the titled compounds **4c** and **7e**. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

Table 2: The zones of inhibition (mm) of the synthesized compounds and standard antimicrobial drugs.

Compound number	Zone of inhibition (mm)						
	Staphylococcus aureus	*Bacillus*	*Escherichia coli*	*Klebsiella*	*Salmonella*	*Pseudomonas*	*Candida*
3a	11 ± 0.186	—	—	—	—	—	—
3b	—	—	—	—	—	—	—
3c	—	—	—	—	—	—	—
3e	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	—
5	16 ± 0.136	13 ± 0.501	—	12 ± 0.42	12 ± 0.075	—	—
4b	—	—	—	—	—	14 ± 0.056	—
4c	—	—	—	—	—	10 ± 0.138	—
6a	15 ± 0.322	15 ± 0.894	—	—	—	—	—
6b	10 ± 0.27	—	—	—	—	—	—
6c	13 ± 0.273	12 ± 0.071	—	—	—	—	—
Ampicillin	30 ± 0.057	15 ± 0.069	25 ± 0.07	13 ± 0.062	34 ± 0.059	18 ± 0.054	—
Fluconazole	—	—	—	—	—	—	38 ± 0.037

Bonev et al. [28]. The antimicrobial activities of the synthesized compounds (**3a–c**, **3e**, **4e**, **4b-c**, **5**, and **6a–c**) were tested against some selected microorganisms, including *Staphylococcus aureus, Bacillus* species, *Escherichia coli, Klebsiella* species, *Salmonella* species, *Pseudomonas* species, and *Candida albicans* (Table 2).

As shown in Table 2, results of the antimicrobial activity studies revealed that the test compounds displayed variable inhibitory effects against the growth of the tested bacteria. Interestingly, compound **6a** was equally potent to ampicillin against *Bacillus* species. The antimicrobial potencies of other derivatives, particularly compound **5** (against *Klebsiella* and *Bacillus*), were potentially comparable to those of ampicillin. The antifungal activity study revealed that the tested compounds exhibited no activity against *Candida albicans*.

3.3.2. Evaluation of Anti-Inflammatory Activity. Compounds **3a–c**, **3e**, **4a–e**, **5**, **6a–c**, and **7a–f** were screened *in vitro* for anti-inflammatory activity, using a method previously described by Mahajan et al. [29]. The anti-inflammatory activity of the thiazole and thiophene derivatives (Table 3) showed that compounds **3e**, **4b**, and **6a** possessed more potent anti-inflammatory activity than that of diclofenac sodium. Compounds **4d** and **7b** showed good anti-inflammatory activity, whereas compounds **5**, **7d**, and **7f** showed moderate activity.

4. Conclusions

In this study, we successfully synthesized some thiazole, pyrimidine, and thiophene derivatives. Among them, fifteen new target compounds were prepared. In addition, seven compounds (**4c**, **7e**) were successfully obtained as pure crystals. Antimicrobial activity studies revealed that the test compounds displayed broad antibacterial spectrum and good potency. Interestingly, compound **6a** was equally potent to ampicillin against *Bacillus* strains. According to the

Table 3: *In vitro* anti-inflammatory activity of the synthesized compounds and standard drug (diclofenac sodium).

Compound number	Spectrophotometer + RBC	Spectrophotometer + RBC (% hemolysis)
3a	0.011 ± 0.0068	101.13 ± 0.0031
3b	0.013 ± 0.000516	102.1542 ± 0.021
3c	0.009 ± 0.000473	102.6048 ± 0.00402
3e	0.179 ± 0.01775	101.6216 ± 0.0005
4d	0.011 ± 0.0068	101.13 ± 0.0031
4e	0.098 ± 0.001227	102.686 ± 0.00211
5	0.101 ± 0.01862	101.9084 ± 0.0002
4a	0.017 ± 0.0075	101.908 ± 0.002404
4d	0.219 ± 0.0225	102.727 ± 0.0126
4c	0.032 ± 0.002	102.441 ± 0.01308
6a	0.146 ± 0.001366	102.523 ± 0.0187
6b	0.01 ± 0.00493	102.154 ± 0.00312
6c	0.046 ± 0.001789	102.236 ± 0.0107
7a	0.023 ± 0.000894	102.0723 ± 0.02135
7b	0.113 ± 0.001033	102.318 ± 0.0042
7c	0.029 ± 0.003225	102.113 ± 0.028
7d	0.066 ± 0.00324	102.2 ± 0.00301
7e	0.052 ± 0.0041	102.154 ± 0.0014
7f	0.06 ± 0.00319	101.908 ± 0.01405
Diclofenac sodium	0.132 ± 0.002251	102.851 ± 0.00076
Control	0.261 ± 0.002683	—
Blank	0.428 ± 0.002442	—

anti-inflammatory activity test, compounds **3e**, **4b**, and **6a** possessed greater anti-inflammatory potency than that of the standard drug. Therefore, compound **6a** was shown to exhibit both antibacterial and anti-inflammatory activities, which could be beneficial in the treatment of various diseases.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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