New Thiophene Derivatives as Antimicrobial Agents

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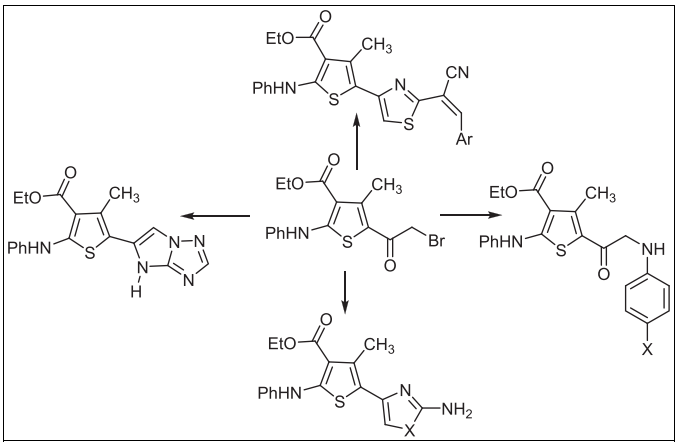

Phenacylbromide derivatives constitute a multilateral group of precursors for the synthesis of numerous heterocycles of organic compounds. Briefly, 5-(2-bromo-acetyl)-substituted-thiophene derivative has been used as a synthon for synthesis of new thiophene-containing compounds through the reaction with nucleophilic nitrogen compounds and thioamides. The suggested structures of the newly synthesized thiophene compounds were confirmed and assured with different spectroscopic tools and with CHN elemental analysis. Additionally, the antimicrobial activity of these thiophene compounds was recorded to investigate their potency against various types of bacteria and fungi. Results showed that these compounds exhibit significant inhibitory activity against the growth of tested bacterial and fungal strains and that some derivatives were more potent than the employed reference drugs.

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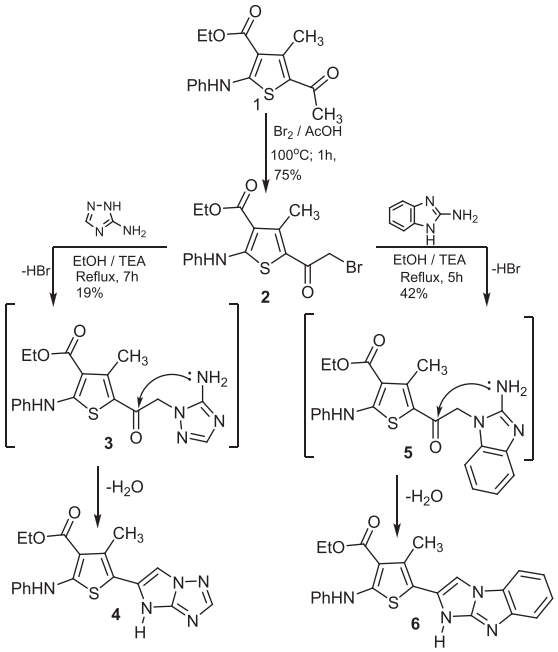
INTRODUCTION

Resistance of the human body to antimicrobial drugs increases the need to discover new drugs against resistant pathogens. In the last decades, much interest has been focused on sulfur analogs, such as thiophene-containing compounds, which showed a very similar classical pharmacological profile. Several thiophene compounds were developed that are superior in potency and their capability to connect to several receptors with high alliance. It is widely found as the core structure in several pharmaceutically active and natural compounds[1–6]. Chiefly, 2-amino-3-substituted-thiophenes are agonist allosteric enhancers at the A1 adenosine receptor[7,8]. A new class of antagonists of the human glucagon receptor for thiophene analogous has been discovered[9]. Moreover, some derivatives of 3-arylthiophene possess anthelmintic activity against *Haemonchus contortus*[10]. The family thiophene-2-carboxylic acid derivatives were found as AMPA receptor allosteric modulators[11,12]. They are significant heterocyclic molecules that are extensively used as precursors in numerous agrochemicals[13]. In addition, several antimicrobial agents carry thiophene ring[14–16]. Accordingly, and owing to the wide range of biological applications of thiophenes, and in continuation to our work on the synthesis of new compounds of pharmacological interest[17–19], we present, herein, the synthesis and characterization of a new series of thiophene-based compounds, along with their antimicrobial activities.

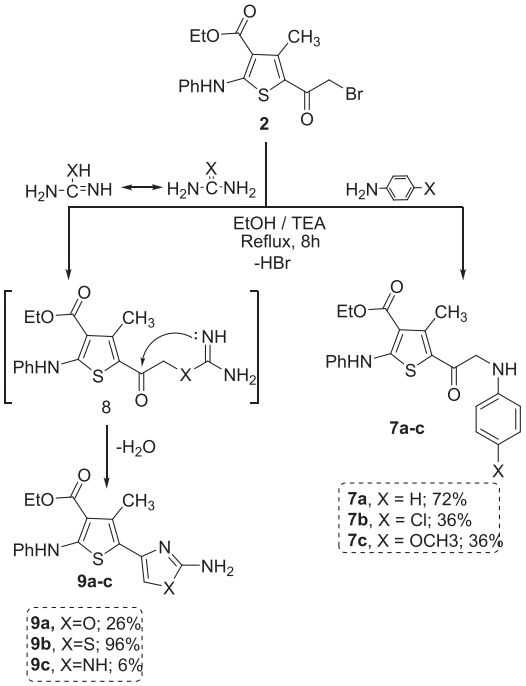
RESULTS AND DISCUSSION

The tetra-substituted-thiophene derivative **2**, a synthon needed in this investigation, was formed as a pale yellow powder through bromination of compound **1** in an acidic medium as sketched in Scheme 1. The suggested structure of the starting compound **2** was confirmed from

Scheme 1. Synthesis of compounds **2**, **4**, and **6**.



Scheme 2. Synthesis of compounds **7a–c** and **9a–c**.

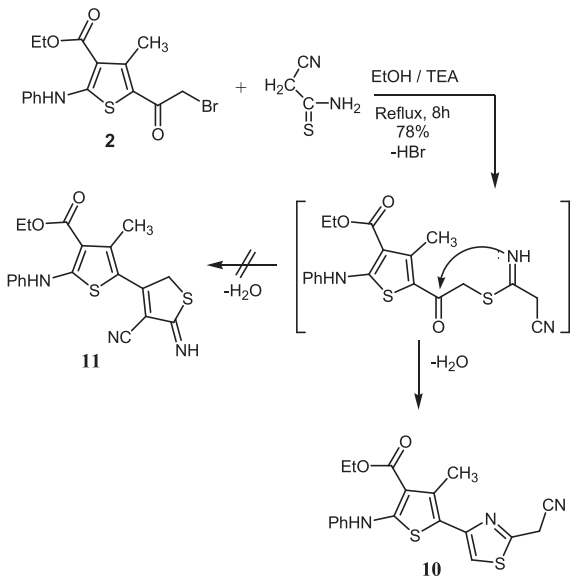


results of its spectra as the ^{1}H-NMR of this compound revealed the presence of a characteristic singlet signal for the bromo-methylene protons at δ 4.69 ppm [20] instead of the methyl group of CH_3CO. Reaction of compound **2** with the heterocyclic amines, 3-amino-1,2,4-triazole, and 2-aminobenzimidazole in ethanol and in the presence of few drops of triethylamine (TEA) under reflux afforded imidazotriazolyl-thiophene derivative **4** and triaza-cyclo penta[α]inden-2-yl)-thiophene derivative **6**, respectively (Scheme 1). Structures of compounds **4** and **6** were determined from their spectral data. All spectral results are in excellent agreement with the purposed structures. As, for example, the IR of both compounds are found free from any absorption bands for ketonic carbonyl group in the starting compound **2** and but revealed the existence of NH absorption bands at 3428 and 4241 cm^{-1}, respectively. Additionally, ^{1}H-NMR of compound **4** confirmed its structure through the appearance of a singlet at 8.36 ppm characteristic of the triazole-H proton[21]. The formation of products **4** and **6** proceeded through the substitution reaction with elimination of HBr to form the two non-isolated intermediates **3** and **5**, respectively. Nucleophilic attack of the nitrogen atom of the amino group to the carbon of the carbonyl group followed by cyclization with elimination of water molecule to give the final thiophene products **4** and **6** as depicted in Scheme 1.

Similarly, and because of the high reactivity of the α-bromoketone derivative **2**, it was further reacted with aromatic amines to give compounds **7a–c** (Scheme 2). Furthermore, reaction of compound **2** with urea or its derivatives in ethanol in the presence of traces of TEA afforded 5-(azolyl)thiophene derivatives **9a–c** (Scheme 2). The latter reaction proceeded via the formation of the intermediate **8** then, which upon elimination of a water molecule yielded the desired compounds **9a–c**. Structures of these newly prepared compounds were confirmed by a panel of spectroscopic methods, such as NMR, IR, and mass spectrometry, and by elemental analysis. The ^{1}H-NMR and ^{13}C-NMR spectra of all prepared compounds are in excellent agreement with the proposed structures. In the ^{1}H-NMR spectra of compounds **9a–c** showed the characteristic singlet signal attributed to NH_2 protons at 4.92–6.52 ppm[22]. Moreover, the IR spectrum of compound **9b** showed the presence of absorption bands of the NH and NH_2 at υ = 3390, 3243, and 3150 cm^{-1}. In addition, mass spectra of the synthesized compounds displayed the correct molecular ions as suggested by their molecular formulas.

On the other side, reaction of **2** with cyanoethanethioamide in refluxing ethanol and in the presence of TEA gave one of the two expected products, the thiazole derivatives **10** and the dithiophene derivative **11**, as depicted in Scheme 3. Spectroscopic results confirmed the formation of **10** rather than **11**. The presence of a singlet signal of H-thiazole proton in ^{1}H-NMR of the product at 7.97 ppm proved the formation of structure of **10**[23].

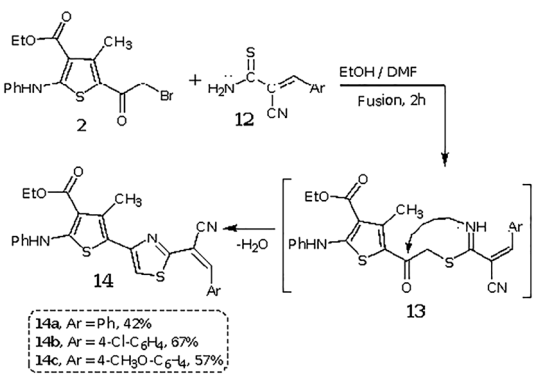
Scheme 3. Synthesis of compound **10**.



Moreover, fusion of phenacylbromide derivative **2** with 2-cyano-3-arylprop-2-enethioamide **12a**–**c** in the presence of a small amount of DMF led to the formation of thiazol-4-yl-thiophene derivatives **14a**–**c** as shown in Scheme 4. The formation of compounds **14a**–**c** proceeds via the S-alkylation intermediate **13** followed by elimination of water molecule as illustrated in Scheme 4. The IR spectra of compounds **14a**–**c** exhibit sharp bands at 2207–2214 cm^{-1} ascribed to the cyano group. Additionally, ^{1}H-NMR spectrum of compound **14b** displayed a singlet at 7.03 ppm that is characteristic of ═CH–Ar[24].

In a similar fashion, reaction between equimolar amounts of tetra-substituted-thiophene derivative **2** and sodium 4-methylbenzenesulfinate in refluxing ethanol afforded 4-methyl-2-phenylamino-5-[2-(toluene-4-sulfonyl)-acetyl]-thiophene-3-carboxylic acid ethyl ester (**15**) via simple substitution reaction with elimination of NaBr molecule (Scheme 5). On the other hand, the hydrazone derivatives **16a**–**c** were obtained via the coupling of compound **15** with diazonium salts of different aromatic amines. Alternatively, the new dithiophene derivative **19** was prepared from the reaction of the salt **17** (synthesized by reaction of pyridine and phenacylbromide derivative **2** in THF under reflux for 2 h)with thioamide derivative in refluxing ethyl alcohol in the presence of drops of TEA (Scheme 5). The spectroscopic information of thiophene derivatives **17** and **19** is in agreement with the suggested structures as illustrated in Scheme 5.

Scheme 4. Synthesis of compounds **14a**–**c**.



ANTIMICROBIAL ACTIVITY

Antimicrobial activity of the new synthesized derivatives was studied according to agar diffusion technique[25], in Al-Azhar University, Cairo, Egypt, at the Regional Center of Mycology and Biotechnology. The newly prepared thiophene derivatives **2**, **4**, **6**, **7a**–**c**, **9b**, **10**, and **14b** were screened for their antifungal and antibacterial (Gram-positive and Gram-negative) activity at 5 μg/mL concentration. The standard antifungal and antibacterial agents (Gram-positive and Gram-negative) employed were amphotericin B, ampicillin, and gentamicin, respectively. The tested fungi were *Aspergillus fumigatus*, *Syncephalastrum racemosum*, *Geotrichum candidum*, and *Candida albicans*. On the other hand, *Streptococcus pneumoniae* and *Bacillus subtilis* were tested for Gram-positive, whereas *Pseudomonas aeruginosa* and *Escherichia coli* were used for Gram-negative bacteria.

The sensitivity of microbial isolates to the tested thiophene derivative was obtained by recording the average diameter of inhibition zones of bacterial growth encirclement the wall (in millimeters) compared with the reference antibiotic used. The results obtained showed variable antimicrobial activity as recorded in Table 1. Noticeably, the *A. fumigatus* and *S. racemosum* showed higher sensitivity towards the test compounds than the other two fungi strains. Among the tested compounds, **9b** and **7b**,**c** were the most potent against *A. fumigatus* with activity 28.1, 26.3, and 24.1 μg/mL, respectively; these compounds were more potent than the reference drug *amphotericin B*. However, compounds **7a**, **4**, and **2** exhibited similar activity of the reference drug *amphotericin B*, whereas the rest of tested compounds displayed moderate activity. For *S. racemosum*, three derivatives **9b**, **4**, and **7b** showed activity higher than that of the reference drug. All tested compounds revealed moderate activity against *G. candidum* and *C. albicans* with an activity range 10.8–19.6 μg/mL.

Scheme 5. Synthesis of compounds **15**, **16**, **17**, and **19**.

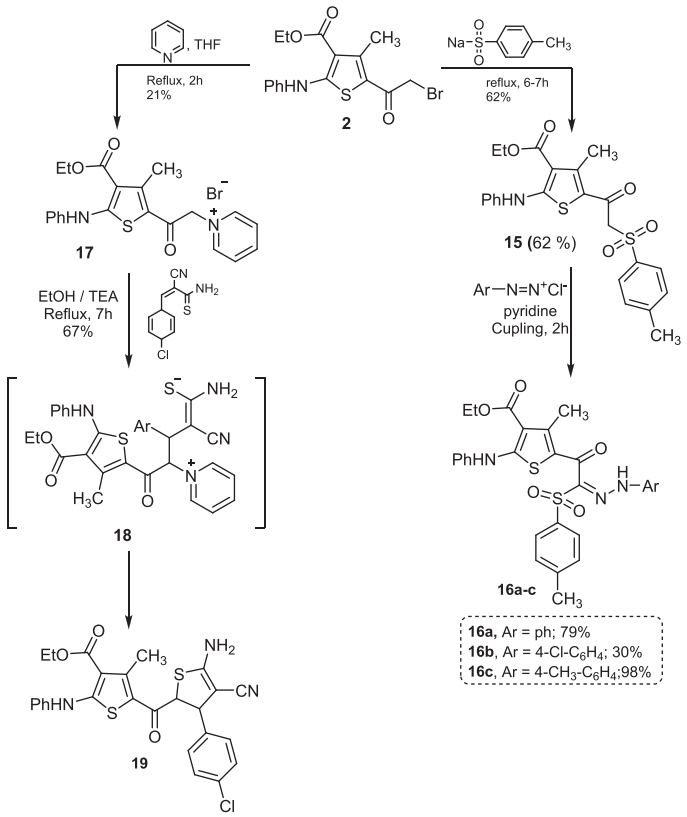


Table 1

Antifungal and antibacterial activity of synthesized compounds (zone of inhibition in diameter in mm).

	Fungi				Gram-positive bacteria		Gram-negative bacteria	
	Aspergillus fumigatus	*Syncephalastrum racemosum*	*Geotrichum candidum*	*Candida albicans*	*Streptococcus pneumoniae*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
St.	Amphotericin B				Ampicillin		Gentamicin	
	23.7 ± 0.1	19.7 ± 0.2	28.7 ± 0.2	25.4 ± 0.1	23.8 ± 0.2	32.4 ± 0.3	17.3 ± 0.1	19.9 ± 0.3
2	20.2 ± 0.28	15.9 ± 0.39	18.7 ± 0.29	15.4 ± 0.28	23.9 ± 0.72	30.1 ± 0.56	18.9 ± 0.46	21.2 ± 0.48
4	21.2 ± 0.62	22.8 ± 0.57	19.6 ± 0.46	12.9 ± 0.58	15.7 ± 0.36	11.2 ± 0.33	15.3 ± 0.46	13.3 ± 0.43
6	18.9 ± 0.43	13.4 ± 0.38	11.6 ± 0.29	12.6 ± 0.42	16.7 ± 0.36	19.2 ± 0.27	13.3 ± 0.36	13.6 ± 0.36
7a	23.4 ± 0.65	16.1 ± 0.53	10.8 ± 0.36	11.9 ± 0.34	18.9 ± 0.63	17.9 ± 0.49	11.4 ± 0.27	10.2 ± 0.41
7b	26.3 ± 0.73	20.9 ± 0.61	12.6 ± 0.54	11.2 ± 0.44	18.2 ± 0.68	18.9 ± 0.64	10.8 ± 0.41	11.1 ± 0.43
7c	24.1 ± 0.51	16.9 ± 0.52	11.5 ± 0.43	10.8 ± 0.46	13.8 ± 0.40	17.2 ± 0.43	11.6 ± 0.36	10.9 ± 0.21
9b	28.1 ± 0.76	23.4 ± 0.77	14.1 ± 0.65	13.2 ± 0.58	12.9 ± 0.63	13.2 ± 0.58	10.7 ± 0.24	11.1 ± 0.43
10	16.3 ± 0.35	14.8 ± 0.46	15.3 ± 0.52	14.3 ± 0.58	14.6 ± 0.58	14.3 ± 0.58	10.2 ± 0.31	8.8 ± 0.24
14b	18.2 ± 0.56	13.7 ± 0.39	19.1 ± 0.45	18.2 ± 0.44	16.3 ± 0.42	19.1 ± 0.51	11.4 ± 0.36	10.7 ± 0.31

A potent activity was recorded for compound **2** against the Gram-positive bacteria *S. pneumonia* and against the two Gram-negative bacteria (Table 1). These activities of compound **2** exceeded the activities for the two references antibiotic *Ampicillin* and *Gentamicin* as shown in Table 1. In short, it should be noted that we have succeeded in increasing the activity of the prepared compounds manufactured against fungi by converting compound **2** to compounds **9b** and **7b**,**c**. Apparently, the presence of an aminothiazole incorporated with a thiophene ring in derivative **9b** dramatically changed the activity of compound **2** to higher value. On the other hand, the antibacterial activity of compound **2** is higher than all of the

synthesized derivatives. This activity can be attributed to the presence of carbonyl group and Br atom at the side chain at position 5 of thiophene ring, which can extra form H-bond with the DNA of microbe.

CONCLUSION

Anyone who reads this research article will find valuable and useful information on the synthesis and characterization of a new series of thiophene derivatives. All new thiophene derivatives structures were assured from the extracted data from their possible spectra. Most designed and synthesized thiophene derivatives have been proven effective antimicrobial agents. Apparently, combining an aminothiazole or aminobenzene derivative with a thiophene ring improves the activity of prepared compounds. On the other hand, the antimicrobial activity of compound **2** is higher than that of synthesized compounds. These findings may suggest that some of the prepared compounds can be candidate antimicrobial agents. However, more work is needed to test the efficacy and toxicity of the prepared compounds before going further.

EXPERIMENTAL

General. All chemical compounds and reagents utilized in this research article were bought from Sigma-Aldrich company (St. Louis, MO) and were used in the reactions without any further refining. A Gallenkamp apparatus for melting point was used to measure all mp of all compounds (Thermo Fisher Scientific, Paisley, UK) in suitable glass capillaries without correction. IR spectra for all new thiophene derivatives were measured through mixing and formation of KBr/substance discs and were recorded on FTIR spectrophotometer 1000 (PerkinElmer FTIR) (PerkinElmer, Waltham, MA). A JEOL ECP 600 NMR spectrometer was used to record the NMR (^{1}H and ^{13}C) spectra made in Tokyo, Japan. This device was operated at 600 MHz in the proper solvent ($CDCl_3$ or DMSO-d_6). Chemical shifts (δ scale) are recorded in ppm units while J values (coupling constants) are obtained in Hz (Hertz). All mass spectra of the new thiophene derivatives were recorded on mass spectrometer (a Shimadzu GCMS-QP-1000 EX, made in Tokyo, Japan) at voltage = 70 eV. CHN elemental analysis of the new thiophene derivatives was obtained on elemental analyzer (a PerkinElmer 2400). Biological investigation of the novel thiophene derivatives was tested at Al-Azhar University, Cairo, Egypt, at the Regional Center for Mycology and Biotechnology in the Medical Mycology Laboratory.

Synthesis of 5-(2-bromo-acetyl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (2). The starting thiophene derivative **2** was formed as a pale yellow powder by dissolving (1.5 g, 5 mmol) of compound **1** in (25 mL) glacial acetic acid. Solution was stirred for 10 min at 100°C followed by addition of bromine (0.26 mL, 5 mmol). Stirring was continued for 1 h at 100°C. The solution was cold to ordinary temperature, and then, it was poured onto ice-cold water. The formed solid was collected by vacuum filtration and recrystallized from EtOH to afford the target thiophene product. Yield (75%); mp 128–130°C. IR (KBr, cm^{-1}) ν_{max} = 3465 (NH), 2984, 1656 (C═O), 1587, 1553, 1496, 1425, 1371, 1236, 1078, 1024. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, 3H, J = 6.1 Hz, $CH_2\underline{CH_3}$), 2.47 (s, 3H, CH_3), 4.36 (q, 2H, J = 6.1 Hz, $\underline{CH_2}CH_3$), 4.69 (s, 2H, $\underline{CH_2}Br$), 7.22–7.51 (m, 5H, Ar–H), 10.65 (s, 1H, N$\underline{H}$–Ph) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 14.7 ($CH_2\underline{C}H_3$), 16.7 (CH_3), 30.7 (CH_2–Br), 61.0 ($\underline{C}H_2CH_3$), 111.1, 117.2, 121.9, 123.6, 133.1, 139.9, 145.3, 162.0 (Ar–C), 165.6, 190.2 (C═O). MS (EIMS) *m/z*: 382 (M^+, 20), 295 (24), 265 (45), 221 (28), 174 (100), 143 (25), 95 (45), 63 (75). *Anal*. calcd. for $C_{16}H_{16}BrNO_3S$ (382.27): N, 3.66; H, 4.22; C, 50.27. Found: N, 3.82; H, 4.10; C, 50.08%.

5-(1*H*-Imidazo[1,2-*b*][1,2,4]triazol-5-yl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (4). This thiophene derivative **4** was formed as a greenish yellow powder by treating compound **2** (0.191 g, 0.50 mmol) with (0.042 g, 0.50 mmol) 3-amino-1*H*-1,2,4-triazole in (10 mL) ethanol as solvent and in the presence of trimethylamine as a base catalyst. The reaction mixture was boiled under reflux for 7 h, and the solid product was collected by vacuum filtration on hot. Yield (19%); mp 181–183°C. IR (KBr, cm^{-1}) ν_{max} = 3428 (NH), 2927, 1658 (C═O), 1585 (C═N), 1548, 1495, 1401, 1373, 1242, 1195, 1074, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, J = 6.1 Hz, $CH_2\underline{CH_3}$), 2.49 (s, 3H, CH_3), 4.33 (q, 2H, J = 6.1 Hz, $\underline{CH_2}CH_3$), 5.55 (s, 1H, imidazole–NH), 7.40–7.65 (m, 5H, Ar–H), 8.36 (s, 1H, triazole–CH), 8.64 (s, 1H, triazole–NH), 10.23 (s, 1H, N$\underline{H}$–Ph) ppm. MS (EIMS) *m/z*: 367 (M^+, 13), 294 (20), 260 (25), 186 (78), 140 (50), 112 (100), 91 (85), 77 (30). *Anal*. calcd. for $C_{18}H_{17}N_5O_2S$ (367.43): N, 19.06; H, 4.66; C, 58.84. Found: N, 19.19; H, 4.39; C, 58.63%.

4-Methyl-2-phenylamino-5-(1*H*-1,3*a*,8-triaza-cyclopenta[*α*]inden-2-yl)-thiophene-3-carboxylic acid ethyl ester (6). This compound was prepared as a brown powder by treating (0.191 g, 0.50 mmol) compound **2** with (0.066 g, 0.50 mmol) 2-aminobenzimidazole in (10 mL) ethanol as solvent and in the presence of TEA as a catalyst. The reaction mixture was boiled with reflux for 5 h, and the solid product was collected by vacuum filtration on hot.

Yield 42%; mp 130–132°C. IR (KBr, cm^{-1}) ν_{max} = 3468, 3241 (NH), 2975, 2926, 1648 (C=O), 1582 (C=N), 1532, 1486, 1402, 1370, 1226, 1191, 1076, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 6.1 Hz, CH_2CH_3), 2.40 (s, 3H, CH_3), 4.29 (q, 2H, J = 6.1 Hz, CH_2CH_3), 6.64 (s, 1H, imidazole–NH), 6.91–7.58 (m, 9H, Ar–H), 7.61 (s, 1H, imidazole–H), 10.19 (s, 1H, NH–Ph) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.4 (CH_2CH_3), 15.4 (CH_3), 59.7 (CH_2CH_3), 109.6, 110.7 (2C), 111.2, 115.9, 119.1 (2C), 120.5, 122.2 (2C), 122.7, 130.0, 131.7 (2C), 132.1, 135.9, 138.5, 143.9, 153.5, 160.7, 164.7 (Ar–C), 189.1 (C=O) ppm. MS (EIMS) *m/z*: 417 (M^++1, 10), 416 (M^+, 60), 197 (100), 182 (30), 155 (20), 91 (95). *Anal*. calcd. for $C_{23}H_{20}N_4O_2S$ (416.50): N, 13.45; H, 4.84; C, 66.33. Found: N, 13.31; H, 4.59; C, 66.15%.

Synthesis of compounds 7a–c. These series of thiophene compounds were produced according to the following general method: A mixture of (0.382 g, 1 mmol) of compound **2** and (0093 g, 1 mmol) aniline, (0.127 g, 1 mmol) *p*-chloroaniline, or (0.123 g, 1 mmol) *p*-anisidine in (10 mL) ethanol and in the presence of TEA (Et_3N) was boiled under reflux for 8 h. The product was filtered on hot and washed with cold ethanol to give the desired derivatives **7a–c** in a pure form. All physical features and data of spectra of all derivatives **7a–c** were recorded below.

4-Methyl-2-phenylamino-5-(2-phenylamino-acetyl)-thiophene-3-carboxylic acid ethyl ester (7a). Yield (72%); beige powder; mp 108–110°C. IR (KBr, cm^{-1}) ν_{max} = 3317, 3465 (NH), 2976, 2928, 1651, 1629 (C=O), 1585, 1547, 1488, 1399, 1374, 1282, 1244, 1195, 1078, 1026. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, 3H, J = 6.1 Hz, CH_2CH_3), 2.47 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 4.36 (q, 2H, J = 6.1 Hz, CH_2CH_3), 7.05–7.50 (m, 10H, Ar–H), 10.30 (s, 1H, NH–CH_2), 10.66 (s, 1H, NH–Ph) ppm. MS (EIMS) *m/z*: 396 (M^++1, 5), 395 (M^+, 10), 86 (100). *Anal*. calcd. for $C_{22}H_{22}N_2O_3S$ (394.49): N, 7.10; H, 5.62; C, 66.98. Found: N, 7.01; H, 5.53; C, 66.79%.

5-[2-(4-Chloro-phenylamino)-acetyl]-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (7b). Yield (36%); beige powder; mp 202–204°C. IR (KBr, cm^{-1}) ν_{max} = 3450, 3320 (NH), 1654 (C=O), 1616 (C=). ^{1}H-NMR (300 MHz, *CDCl$_3$*) δ: 1.40 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.74 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.36 (q, 2H, J = 6.0 Hz, CH_2CH_3), 6.53–7.55 (m, 9H, Ar–H), 10.65 (s, 1H, NH), 10.92 (s, 1H, NH–CH_2) ppm. *Anal*. calcd. for $C_{22}H_{21}ClN_2O_3S$ (428.93): N, 6.53; H, 4.94; C, 61.60. Found: N, 6.34; H, 4.75; C, 61.52%.

5-[2-(4-Methoxy-phenylamino)-acetyl]-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (7c). Yield (36%); greenish yellow powder; mp 184–186°C. IR (KBr, cm^{-1}) ν_{max} = 3451, 3348 (NH), 1650 (C=O), 1632 (C=O). ^{1}H-NMR (300 MHz, *CDCl$_3$*) δ: 1.42 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.46 (s, 3H, CH_3), 3.75 (s, 3H, O–CH_3), 3.80 (s, 2H, CH_2), 4.36 (q, 2H, J = 6.0 Hz, CH_2CH_3), 6.60–7.55 (m, 9H, Ar–H), 10.65 (s, 1H, NH), 10.97 (s, 1H, NH–CH_2) ppm. *Anal*. calcd. for $C_{23}H_{24}N_2O_4S$ (424.51): N, 6.60; H, 5.70; C, 65.07. Found: N, 6.46; H, 5.61; C, 64.94%.

Synthesis of compounds 9a–c. The following procedure was employed for the synthesis of compounds **9a–c**: Compound **2** (0.382 g, 1 mmol) was treated with the appropriate (1 mmol) urea derivatives in (10 mL) ethanol as solvent and in the presence of trimethylamine as a catalyst. The mixture was refluxed at 80°C for 8 h. The solid was filtered on hot and recrystallized from ethanol to afford the desired product. Using the same general procedure, the following compounds were prepared.

5-(2-Amino-oxazol-5-yl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (9a). Yield (26%); beige powder; mp 128–130°C. IR (KBr, cm^{-1}) ν_{max} = 3427, 3142 (NH and NH_2), 3091, 1656 (C=O), 1586 (C=N). ^{1}H-NMR (300 MHz, *DMF-d$_7$*) δ: 1.39 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.48 (s, 3H, CH_3), 4.38 (q, 2H, J = 6.1 Hz, CH_2CH_3), 4.92 (s, br, 2H NH_2), 7.50–7.70 (m, 6H, Ar–H + oxazole–H), 10.43 (s, 1H, NH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.2 (CH_2CH_3), 16.1 (CH_3), 60.8 (CH_2CH_3), 110.1, 110.4, 111.4, 122.9, 123.0, 130.1, 132.8, 140.0, 145.0, 151.0, 160.6 (Ar–C), 189.8 (C=O) ppm. *Anal*. calcd. for $C_{17}H_{17}N_3O_3S$ (343.40): N, 12.24; H, 4.99; C, 59.46. Found: N, 12.10; H, 4.85; C, 59.31%.

5-(2-Amino-thiazol-5-yl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (9b). Yield (96%); beige powder; mp 210–212°C. IR (KBr, cm^{-1}) ν_{max} = 3399, 3243, 3150 (NH and NH_2), 2974, 2926, 1645 (C=O), 1586 (C=N), 1525, 1493, 1402, 1373, 1343, 1244, 1197, 1113, 1073. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, 3H, J = 6.1 Hz, CH_2CH_3), 2.45 (s, 3H, CH_3), 4.26 (q, 2H, J = 6.1 Hz, CH_2CH_3), 6.52 (s, 2H, NH_2), 7.13 (s, 1H, thiazole–CH), 7.26–7.55 (m, 5H, Ar–H), 9.92 (s, 1H, NH–Ph) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.2 (CH_2CH_3), 15.4 (CH_3), 59.6 (CH_2CH_3), 100.5, 110.0, 113.9, 116.2, 118.0, 120.1, 120.4, 130.1, 131.8, 140.0, 140.2, 164.9 (Ar–C), 166.9 (C=O) ppm. MS (EIMS) *m/z*: 359 (M^+, 10), 344 (35), 327 (15), 172 (25), 140 (50), 43 (100), 43 (100%). *Anal*. calcd. for $C_{17}H_{17}N_3O_2S_2$ (359.47): N, 11.69; H, 4.77; C, 56.80. Found: N, 11.44; H, 4.63; C, 56.65%.

5-(2-Amino-3H-imidazol-4-yl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (9c). Yield (16%); pale beige powder; mp 90–92°C. IR (KBr, cm^{-1}) ν_{max} = 3404, 3216, 3165 (NH and NH_2), 3165, 1656 (C=O), 1618 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.41 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.74 (s, 3H, CH_3), 4.36 (q, 2H, J = 6.0 Hz, CH_2CH_3), 4.93 (s, br, NH_2), 7.13–7.51 (m, 5H, Ar–H), 10.16, 10.64 (s, 1H, NH) ppm.

Anal. calcd. for $C_{17}H_{18}N_4O_2S$ (342.42): N, 16.36; H, 5.30; C, 59.63. Found: N, 16.23; H, 5.17; C, 59.42%.

5-(2-Cyanomethyl-thiazol-4-yl)-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (10). This thiophene derivative **10** was produced as a black powder from the reaction of derivative **2** (0.382 g, 1 mmol) with (0.1 g, 1 mmol) 2-cyanoethanethioamide in (10 mL) ethanol in the presence of trimethylamine (Et_3N) as a base catalyst and refluxed for 8 h. Collection of the solid product by vacuum filtration of the hot reaction mixture and washed with ethanol to give thiophene compound **10** in a pure form black powder; mp 140–142°C. Yield (78%). IR (KBr, cm^{-1}) ν_{max} = 3423 (NH), 2981, 2193 (CN), 1654 (C═O), 1587 (C═N), 1550, 1495, 1401, 1370, 1235, 1023. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 6.1 Hz, $CH_2C\underline{H}_3$), 2.50 (s, 3H, CH_3), 3.80 (s, 2H, CH_2–CN), 4.22 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 7.29–7.79 (m, 5H, Ar–H), 7.97 (s, 1H, thiazole–H), 9.96 (s, 1H, N$\underline{H}$–Ph) ppm. MS (EIMS) *m/z*: 384 (M^++1, 20), 383 (M^+, 100), 274 (10), 234 (10), 170 (99), 149 (21), 127 (20), 90 (5), 77 (5). *Anal*. calcd. for $C_{19}H_{17}N_3O_2S_2$ (383.49): N, 10.96; H, 4.47; C, 59.51. Found: N, 10.75; H, 4.28; C, 59.36%.

Synthesis of compounds 14a–c. Compound **14a** was prepared by fusion of compound **2** (0.19 g, 0.5 mmol) with 2-cyano-3-phenylprop-2-enethioamide (0.094 g, 0.5 mmol) in the presence of small amount of DMF. Ethanol was then added, and a precipitate was formed that was collected by filtration and recrystallized from mixture of DMF–EtOH to give the desired thiophene compound in pure form. Compounds **14b** and **14c** were prepared by reaction of compound **2** (0.191 g, 0.5 mmol) with 2-cyano-3-(4-chlorophenyl)prop-2-enethioamide (0.191 g, 0.5 mmol) and 2-cyano-3-(4-methoxyphenyl)prop-2-enethioamide (0.109 g, 0.5 mmol), respectively, under the same reaction conditions used in the preparation of compound **14a**.

5-[2-(1-Cyano-2-phenyl-vinyl)-thiazol-4-yl]-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (14a). Yield (42%); deep brown powder; mp 160–161°C. IR (KBr, cm^{-1}) ν_{max} = 3465 (NH), 2209 (CN), 1654 (C═O), 1564 (C═N). ^{1}H-NMR (300 MHz, DMSO-d_6: $CDCl_3$) δ: 1.32 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.64 (s, 3H, CH_3), 4.27 (q, 2H, J = 6.0 Hz, $C\underline{H}_2CH_3$), 6.93–7.58 (m, 12H, Ar–H, ═CH and thiazole–H), 10.53 (s, 1H, NH) ppm. *Anal*. calcd. for $C_{26}H_{21}N_3O_2S_2$ (471.59): N, 8.91; H, 4.49; C, 66.22. Found: N, 8.73; H, 4.25; C, 66.06%.

5-{2-[2-(4-Chloro-phenyl)-1-cyano-vinyl]-thiazol-4-yl}-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (14b). Yield (67%); deep brown powder; mp 170–171°C. IR (KBr, cm^{-1}) ν_{max} = 3368 (NH), 3059, 2927, 2214 (CN), 1680 (C═O), 1618, 1546 (C═N), 1494, 1414, 1239, 1195, 1026. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, 3H, J = 6.1 Hz, $CH_2C\underline{H}_3$), 2.47 (s, 3H, CH_3), 4.37 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 7.08–7.54 (m, 10H, Ar–H and ═CH), 8.01 (s, 1H, thiazole–H), 10.65 (s, 1H, N$\underline{H}$–Ph) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 ($CH_2\underline{C}H_3$), 16.8 (CH_3), 60.8 ($\underline{C}H_2CH_3$), 108.0 (NC-$\underline{C}$═), 110.0, 119.0, 120.3, 121.7, 129.3, 129.5, 129.7, 130.0, 132.5, 132.7, 139.1, 119.0 (CN), 120.3, 132.7 (C═C, thiazole), 146.2 (═C-Ph), 163.1 (C═N), 163.3 (Ar–C), 167.9 (C═O). *Anal*. calcd. for $C_{26}H_{20}ClN_3O_2S_2$ (506.04): N, 8.30; H, 3.98; C, 61.71. Found: N, 8.16; H, 3.87; C, 61.58%.

5-{2-[1-Cyano-2-(4-methoxy-phenyl)-vinyl]-thiazol-4-yl}-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (14c). Yield (57%); deep brown powder; mp 130–131°C. IR (KBr, cm^{-1}) ν_{max} = 3465 (NH), 2207 (CN), 1655 (C═O), 1585 (C═N). ^{1}H-NMR (300 MHz, DMF-d_7) δ: 1.39 (t, 3H, J = 6.0 Hz, $CH_2C\underline{H}_3$), 2.48 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 4.38 (q, 2H, J = 6.0 Hz, $C\underline{H}_2CH_3$), 6.85–7.81 (m, 11H, Ar–H, ═CH and thiazole–H), 10.43 (s, 1H, NH) ppm. *Anal*. calcd. for $C_{27}H_{23}N_3O_3S_2$ (501.62): N, 8.38; H, 4.62; C, 64.65. Found: N, 8.21; H, 4.39; C, 64.43%.

4-Methyl-2-phenylamino-5-[2-(toluene-4-sulfonyl)-acetyl]-thiophene-3-carboxylic acid ethyl ester (15). This compound was prepared as a yellow powder according to the following procedure: Compound **2** (0.382 g, 1 mmol) was treated with sodium 4-methylbenzenesulfinate (0.178 g, 1 mmol) in 10 mL of ethanol as solvent. The mixture was heated under reflux for 6–7 h, and the precipitate was collected by filtration, washed with water, and recrystallized from ethanol to afford compound **15**, which was used later for other reactions. Because of its partial solubility in DMSO-d_6 we could not obtain a good ^{13}C-NMR spectrum of the compound. Yield (62%); mp 224–226°C. IR (KBr, cm^{-1}) ν_{max} = 3414 (NH), 1658 (C═O), 1594 (S═O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 6.1 Hz, $CH_2C\underline{H}_3$), 2.37 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.30 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 4.86 (s, 2H, CH_2), 7.62–7.75 (m, 9H, Ar–H), 10.20 (s, 1H, N$\underline{H}$–Ph) ppm. MS (EIMS) *m/z*: 457 (M^+, 5), 305 (30), 155 (80), 139 (15), 91 (100), 77 (10), 65 (20). *Anal*. calcd. for $C_{23}H_{23}NO_5S_2$ (457.56): N, 3.06; H, 5.07; C, 60.37. Found: N, 3.19; H, 5.17; C, 60.25%.

Synthesis of compounds 16a–c. Compounds **16a–c** were synthesized according to the following general procedure: Compound **15** (0.220 g, 0.5 mmol) was dissolved in pyridine (10 mL), and the solution was placed in an ice bath with continuous stirring at 0–5°C until complete dissolution. Drops of substituted benzendiazonium chloride, prepared by treatment of aniline, *p*-chloroaniline, or *p*-toluidine (1 mmol) with an equivalent amount of conc. hydrochloric acid (1 g, 3 mL) at 0°C, followed by addition of sodium nitrite solution with stirring. The mixture was placed in a refrigerator for 12 h until a precipitate was formed, which was collected

by filtration and recrystallized from ethanol. Using this general procedure, the following compounds were prepared.

4-Methyl-2-phenylamino-5-[2-(phenyl-hydrazono)-2-(toluene-4-sulfonyl)-acetyl]-thiophene-3-carboxylic acid ethyl ester (16a). Yield (79%); reddish brown needles; mp > 300°C. IR (KBr, cm^{-1}) ν_{max} = 3162, 3466 (NH), 2985, 1656 (C═O), 1587 (S═O), 1552 (C═N), 1496, 1427, 1400, 1370, 1344, 1235, 1024. ^{1}H-NMR (300 MHz, CF_3COOD) δ: 1.43 (t, 3H, J = 6.1 Hz, $CH_2\underline{CH}_3$), 2.63 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 4.47 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 7.24–8.25 (m, 14H, Ar–H), 8.47 (s, 1H, NH), 11.46 (s, 1H, NH) ppm. *Anal*. calcd. for $C_{29}H_{27}N_3O_5S_2$ (561.67): N, 7.48; H, 4.85; C, 62.01. Found: N, 7.31; H, 4.97; C, 62.23%.

5-[2-[(4-Chloro-phenyl)-hydrazono]-2-(toluene-4-sulfonyl)-acetyl]-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (16b). Reddish brown powder. Yield (30%); mp > 300°C. IR (KBr, cm^{-1}) ν_{max} = 3212, 3449 (NH), 1656 (C═O), 1635 (C═O), 1559 (C═N). ^{1}H-NMR (300 MHz, *CDCl$_3$*) δ: 1.41 (t, 3H, J = 6.0 Hz, $CH_2\underline{CH}_3$), 2.46 (s, 3H, CH_3), 2.90 (s, 3H, CH_3–Ph), 4.38 (q, 2H, J = 6.0 Hz, $C\underline{H}_2CH_3$), 6.20–7.56 (m, 13H, Ar–H), 10.64 (s, 1H, NH), 10.87 (s, 1H, NH) ppm. *Anal*. calcd. for $C_{29}H_{26}ClN_3O_5S_2$ (596.12): N, 7.05; H, 4.40; C, 58.43. Found: N, 6.89; H, 4.39; C, 58.26%.

4-Methyl-2-phenylamino-5-[2-(toluene-4-sulfonyl)-2-(p-tolyl-hydrazono)-acetyl]-thiophene-3-carboxylic acid ethyl ester (16c). Yield (98%); reddish brown powder. IR (KBr, cm^{-1}) ν_{max} = 3205, 3451 (NH), 1656 (C═O), 1630 (C═O), 1554 (C═N); mp > 300°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.42 (t, 3H, J = 6.0 Hz, $CH_2\underline{CH}_3$), 2.47 (s, 3H, CH_3), 2.74 (s, 3H, CH_3–Ph), 2.86 (s, 3H, CH_3–Ph), 4.39 (q, 2H, J = 6.0 Hz, $C\underline{H}_2CH_3$), 7.21–7.59 (m, 13H, Ar–H), 10.65 (s, 1H, NH), 10.87 (s, 1H, NH) ppm. *Anal*. calcd. for $C_{30}H_{29}N_3O_5S_2$ (575.70): N, 7.30; H, 5.08; C, 62.59. Found: N, 7.43; H, 5.12; C, 62.38%.

1-[2-(4-Ethoxycarbonyl-3-methyl-5-phenylamino-thiophen-2-yl)-2-oxo-ethyl]-pyridinium bromide (17). This salt was prepared by dissolving compound **2** (0.382 g, 1 mmol) in THF (20 mL). The mixture was heated under reflux until the solid dissolved, then pyridine (1 mmol) was added, and the mixture was refluxed for 2 h. The solid produced was collected by filtration while hot to afford the desired compound in a pure form, which was then used in a subsequent reaction. Yield (21%); yellow powder; mp 220–222°C. IR (KBr, cm^{-1}) ν_{max} = 3423 (NH), 2999, 2925, 1660 (C═O), 1626 (C═O), 1580 (C═N), 1543, 1477, 1408, 1369, 1238, 1198. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.98 (t, 3H, J = 6.1 Hz, $CH_2\underline{CH}_3$), 2.50 (s, 3H, CH_3), 4.07 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 5.87 (s, 2H, CH_2), 7.33–7.61 (m, 5H, Ar–H), 8.15–8.93 (m, 5H, Pyridine-H), 9.78 (s, 1H, N$\underline{H}$–Ph) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.9 ($CH_2\underline{C}H_3$), 16.7 (CH_3), 60.6 ($\underline{C}H_2CH_3$), 66.7 ($\underline{C}H_2$-pyridine), 109.9, 120.7, 122.3, 125.3, 127.1, 127.2, 129.5, 132.3, 138.9, 145.6, 164.2 (Ar–C), 165.7, 180.7 (C═O) ppm. *Anal*. calcd. for $C_{21}H_{21}BrN_2O_3S$ (461.37): N, 6.07; H, 4.59; C, 54.67. Found: N, 6.14; H, 4.60; C, 54.49%.

5-[5-Amino-3-(4-chloro-phenyl)-4-cyano-2,3-dihydro-thiophene-2-carbonyl]-4-methyl-2-phenylamino-thiophene-3-carboxylic acid ethyl ester (19). Derivative **19** was formed according to the following method: A mixture of the salt **17** (0.23 g, 0.5 mmol) and 4-Cl-3-(phenyl)-2-cyanoprop-2-enethioamide (0.5 mmol) in ethanol (10 mL) and in the presence of TEA as a catalyst was refluxed for 7 h. The solid product was collected by filtration while hot to afford the desired compound in pure form. Yield (67%); reddish brown powder; mp > 300°C. IR (KBr, cm^{-1}) ν_{max} = 3423, 3337, 3269 (NH and NH_2), 2369 (CN), 1653 (C═O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, 3H, J = 6.1 Hz, $CH_2\underline{CH}_3$), 2.46 (s, 3H, CH_3), 4.35 (q, 2H, J = 6.1 Hz, $C\underline{H}_2CH_3$), 4.49 (d, 1H, dihydrothiophene–H), 4.94 (d, 1H, dihydrothiophene–H), 4.97 (s, 2H, NH_2), 7.21–7.50 (m, 9H, Ar–H), 10.65 (s, 1H, N$\underline{H}$–Ph) ppm. Anal. calcd. for $C_{26}H_{22}ClN_3O_3S_2$ (524.05): N, 8.02; H, 4.23; C, 59.59. Found: N, 8.22; H, 4.15; C, 59.71%.

Antimicrobial evaluation using agar diffusion technique. The method used for evaluation the antimicrobial activity of the new synthesized thiophene derivatives **2**, **4**, **6**, **7a–c**, **9b**, **10**, and **14b** was described briefly by Cruickshank et al[25].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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