Synthesis of new heterocycles festooned with thiophene and evaluating their antioxidant activity

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Abstract

The chemical performance of 5-bromo-2-(bromoacetyl)-thiophene (**1**) was tested towards the reaction with numerous bi-nucleophilic reagents (namely; 2-aminobenzothiazoles, 2-aminothiazole, 2-aminotetrazole, 2-aminotriazole, 2-aminopyridines, 2-aminobenzimidazole and *o*-phenylenediamine). Therefore, a series of bridged nitrogen heterocycles bearing thiophene moiety **3**, **5**, **7**, **9**, **11**, **13** and **15**, respectively was synthesized. In addition, the reaction of 5-bromo-2-(bromoacetyl)-thiophene with the thiocarbamoyl compounds **17**, **19** and/or **24** afforded the corresponding thienyl-thiazoles **18** or dithien-2-yl ketones **20** and **25**, based on the reaction conditions. Treatment of **1** with 2-mercapto-4,6-dimethylnicotinonitrile was achieved to obtain the target dithien-2-yl ketone **28**. The new synthesized scaffolds were examined for their antioxidant activity by means of ABTS antioxidant assay. The thienyl-thiazole scaffold **18c** and 2-((2-(thiophen-2-yl)-2-oxoethyl)thio)nicotinonitrile derivative **27** displayed a reasonable radical scavenging activity.

1 | INTRODUCTION

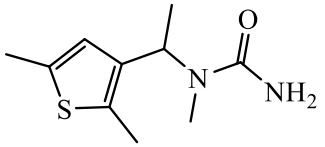
As problems of world's health growth and population increases discovering novel therapeutics will be even more substantial. The drug design scaffolds conceivable shows approximately the greatest prospect aimed at achievement in current and the future period. The study for novel scaffolds owing properties of antioxidant is very important area of the research, so they able to protect human body from attacking by free radical and hinder the development of several long-lasting diseases for example cancer, vascular and the oxidative stress diseases responsible for protein, DNA and also membrane destruction behaviors.[1,2] The heterocyclic scaffolds are broadly spread in nature and necessary for the life, there are

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4122

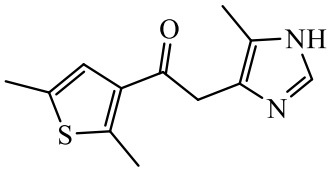
massive many pharmacologically active heterocyclic moieties numerous of that are in consistent clinical use.

Substituted thiophenes are considered as a one of the more significant aromatic heterocyclic derivatives. They concerned the attention of biologists and chemists because of their extensive range of biological activities and its application as a synthetic intermediate. Numerous molecules including thiophene moiety displayed significant pharmacological interests particularly antioxidant activity.[3–6] 3-Cyano-2,4-diaminothiophenes were identified as maternal embryonic leucine zipper kinase (MELK) inhibitors.[7] Moreover, thiophene derivatives find large application in coordination chemistry,[8,9] material science[10–20] and as potential intermediate in organic synthesis.[21,22] In addition, the imidazole ring is commonly existing in many synthetic and natural products. One of the structural advantages of imidazole moiety is that it readily binds to various receptors and enzymes in biological systems. Thus, fused imidazole heterocycles displaying broad bioactivities like anticonvulsant[23] anti-inflammatory,[24] sodium channel blocking,[25] antimicrobial,[26] anticancer,[27-29] CB1 receptor and antihypertensive properties.[30] For example, imidazo[2,1-*b*]thiazole-guanylhydrazone derivative (**III**) (Figure 1) is considered as promising drug compound which displayed effective antiproliferative activity against many cancer cell lines. Substituted 7,8-dihydro-imidazo[2,1-*b*]benzothiazol-5-one derivatives were screened for their virus-inhibiting activity against influenza A virus.[31]

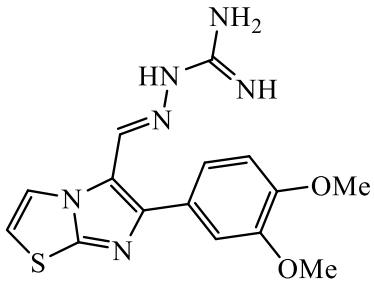
Depending on the significant pharmacological interests mainly antioxidant activity of substituted thiophenes, there is a strong inspiration for the continuous synthesis of new heterocyclic systems incorporating substituted thiophene moiety. Therefore, further continuation of our previous work,[32-36] we are informing here the synthesis of some more analogues of various heterocyclic systems (namely; imidazo-thiazole, imidazo-tetrazole, imidazo-triazole, imidazo-pyridine, imidazo-imidazole, thiazole and/or thiophene) incorporating 2-thienyl moiety and evaluating their in vitro anti-oxidant activity.



I (anti-inflammatory activity)



II (Alzheimer's disease treatment)



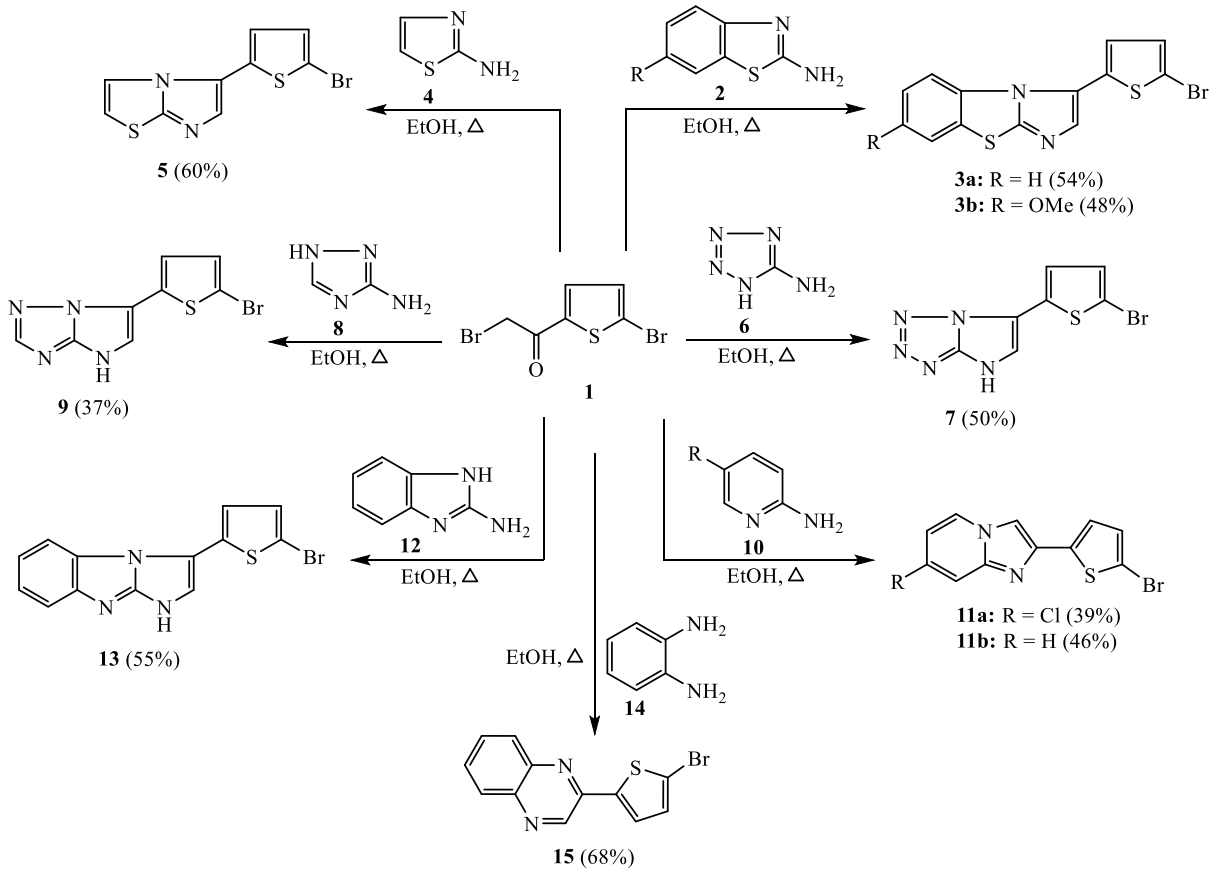
III (antiproliferative activity)

FIGURE 1 Examples of biologically active thiophene and imidazole compounds

2 | RESULTS AND DISCUSSION

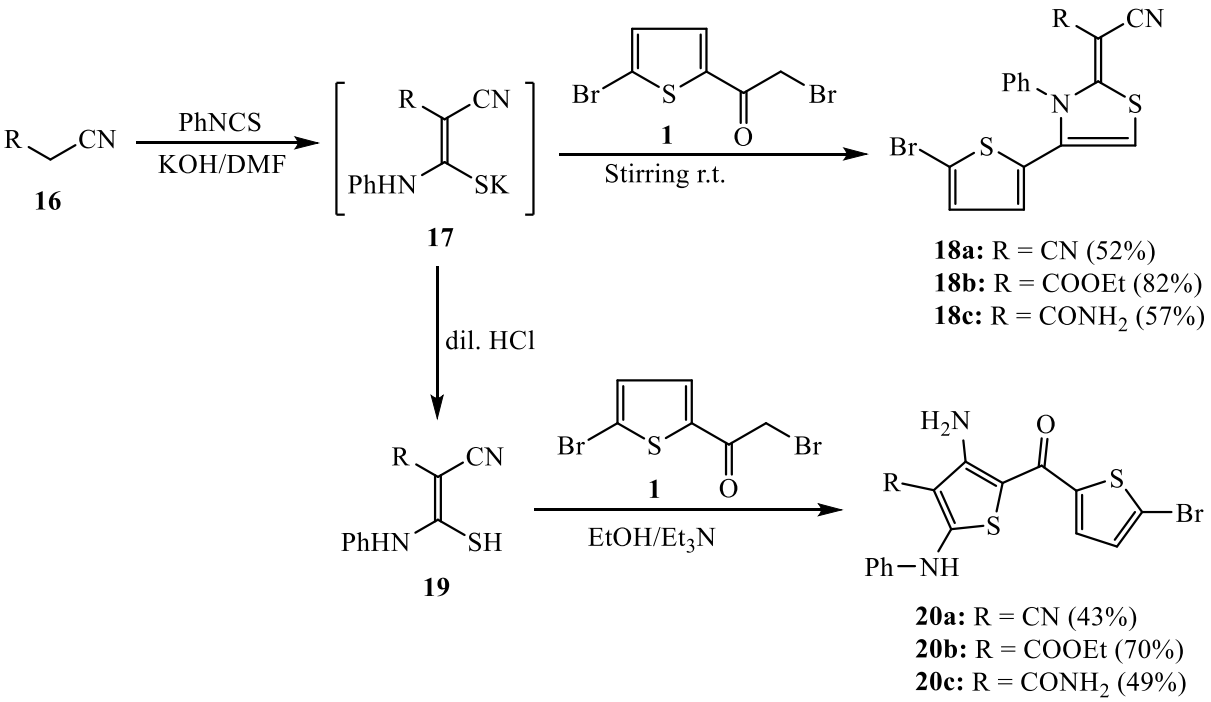
2.1 | CHEMISTRY

The highly versatile α-bromocarbonyl reagent, 5-bromo-2-(bromoacetyl)-thiophene (**1**), has been prepared by the reported conditions through the free radical bromination of 2-acetylthiophene substrate.[37] The chemical behavior of 5-bromo-2-(bromoacetyl)-thiophene (**1**) was verified towards the reaction with several bi-nucleophilic reagents in order to prepare several bridge nitrogen compounds. Thus, 5-bromo-2-(bromoacetyl)-thiophene (**1**) was heated with 2-aminobenzothiazole derivatives **2**, 2-aminothiazole (**4**), 2-aminotetrazole (**6**), 2-aminotriazole (**8**), 2-aminopyridine derivatives **10**, 2-aminobenzimidazole (**12**) and/or *o*-phenylenediamine (**14**) in absolute ethanol in a non-catalyzed reaction. The reaction afforded a series of the corresponding nitrogen containing heterocycles bearing thiophene moiety, namely; imidazo-thiazoles **3** and **5**, imidazo-tetrazole **7**, imidazo-triazole **9**, imidazo-pyridines **11**, imidazo-imidazole **13** and quinoxaline **15**, respectively (Scheme 1). The chemical structures of the synthesized scaffolds were demonstrated by standard spectroscopic data such as IR, ^{1}H NMR, ^{13}C NMR and mass analyses.



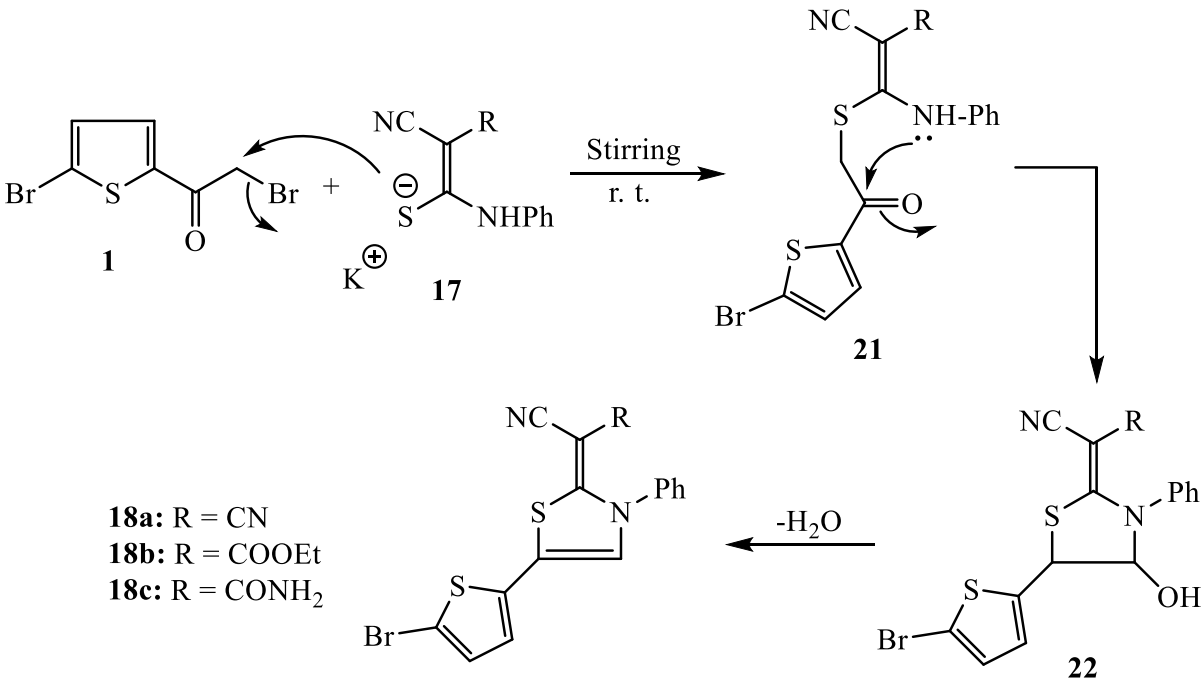
SCHEME 1 Synthesis of thienyl-fused heterocyclic compounds **3**, **5**, **7**, **9**, **11**, **13** and **15**

In the course of our investigation, a synthetic route was established to the synthesis of thiazoles, which consider a privileged structure for its antioxidant activity[38] and the thiophene moiety. The treatment of activated nitriles **16** (namely; malononitrile, ethyl cyanoacetate and cyanoacetamide) with phenyl isothiocyanate was carried out by stirring in dimethylformamide in the presence of potassium hydroxide to afford the highly activated potassium sulfide intermediates **17**. *In situ* treatment of **17** with 5-bromo-2-(bromoacetyl)-thiophene (**1**) promoted heterocyclization to obtain a series of thiazole bearing thiophene scaffolds **18a**, **18b** and **18c** in good yields (Scheme 2). On the other hand, acidification of potassium sulfide intermediates **17** with dilute HCl furnished their corresponding thiocarbamoyl derivatives **19**. The reaction of **19** with 5-bromo-2-(bromoacetyl)-thiophene (**1**) was achieved in boiling ethanol and triethylamine to present different cyclization behavior and afforded the di-thien-2-yl ketones **20a**, **20b** and **20c** in good yields (Scheme 2).



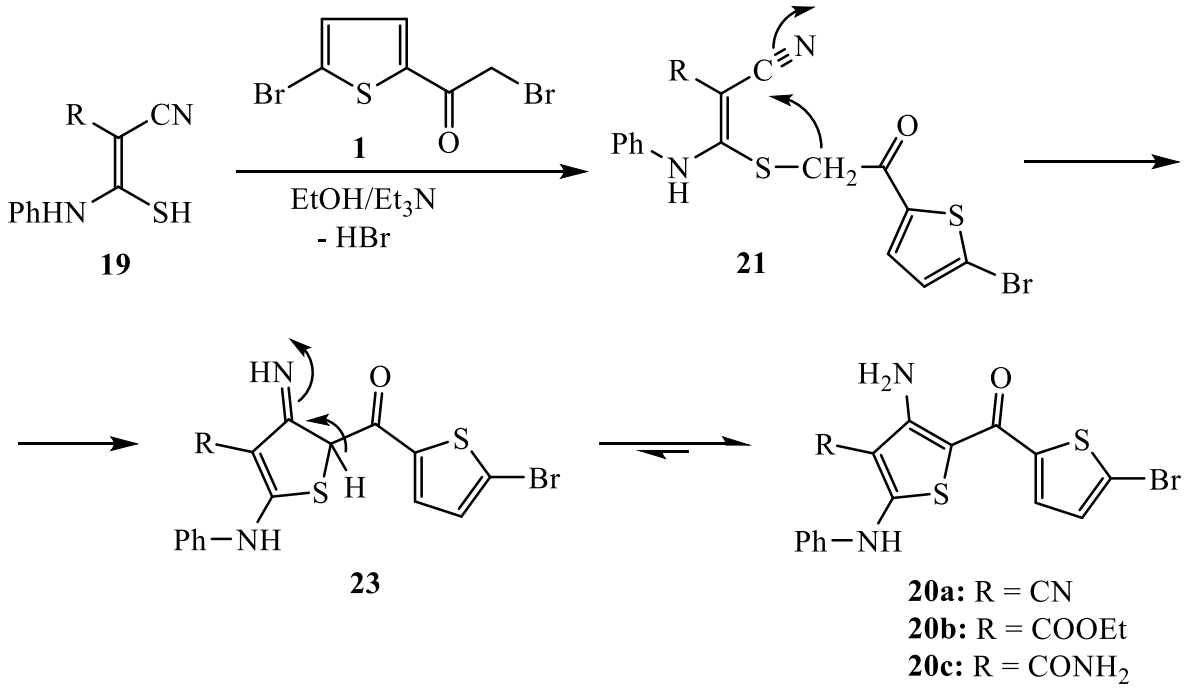
SCHEME 2 Synthesis of thienyl-thiazole and dithienyl-ketone compounds **18** and **20**

The reaction mechanism illustrating the establishment of compounds **18a**, **18b** and **18c** hypothesized by the authors is depicted in (Scheme 3). In a first step, the sulfide nucleophile can be readily attacking the α-carbon carrying the bromide atom in a bimolecular nucleophilic substitution reaction to give the intermediate **21**, which is not stable and undergo intramolecular heterocyclization through the nucleophilic nitrogen-affording compound **22**. Dehydration of **22** results in the formation of the scaffolds **18a**, **18b** and **18c**.



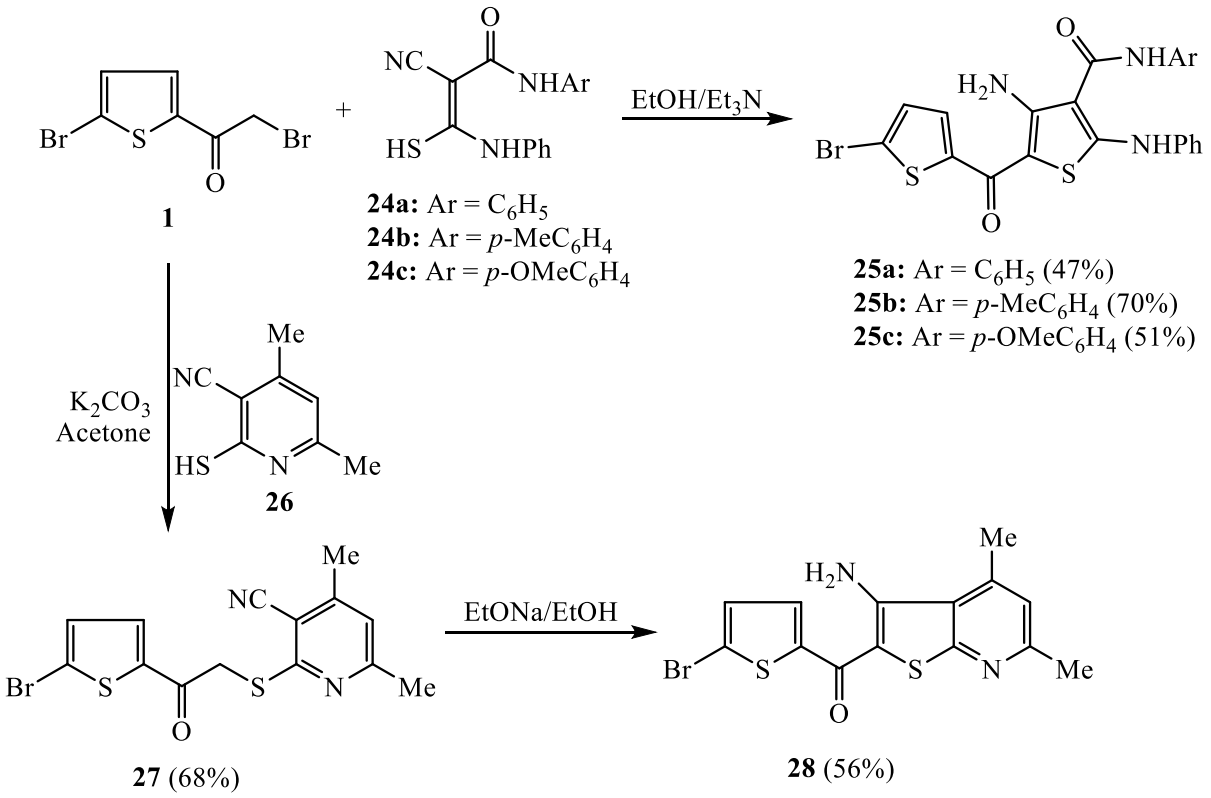
SCHEME 3 Reaction mechanism for the formation of thienyl-thiazole compounds **18a-c**

The open-chain precursor **21** is also the intermediate for treatment of 5-bromo-2-(bromoacetyl)-thiophene (**1**) with the thiocarbamoyl nucleophiles **19** under reflux in absolute ethanol and triethylamine. The authors described the synthesis of the di-thien-2-yl ketones scaffolds **20a**, **20b** and **20c** depending on the tendency of the open-chain precursors **21** to undergo *in situ* heterocyclization through nucleophilic addition of methylene group to the carbonyl group and elimination of water molecule (Scheme 4).



SCHEME 4 Reaction mechanism for the formation of dithien-2-yl ketones **20a-c**

In line with our research plan, the highly functionalized dithien-2-yl ketones **25a**, **25b** and **25c** were obtained as the main products, on treating thiocarbamoyl derivatives **24** with 5-bromo-2-(bromoacetyl)-thiophene (**1**) in the presence of ethanol and triethylamine as a catalyst (Scheme 5). In view of the extensive and increasing interest in the pharmaceutical activities of pyridine containing scaffolds, we investigated the reaction of **1** with 2-mercapto-4,6-dimethylnicotinonitrile (**26**) by heating in acetone and potassium carbonate to furnish the corresponding sulfide **27**. The formation dithien-2-yl ketone of the type **28** was achieved via boiling the open-chain precursor **27** in ethanolic sodium ethoxide solution.



SCHEME 5 Synthesis dithien-2-yl ketones **25a-c** and **28**

2.2. | Assessment of antioxidant activity

Reactive oxygen species (ROS) and Free radicals are extremely responsive and can be produced by regular cellular processes. Cell components respond with ROS inspire mutilation of proteins, lipids, DNA and carbohydrates are involved with several diseases, including diabetes, cancer and atherosclerosis. In current years, researchers in the area of medicinal chemistry motived to the synthesis of numerous thiophene derivative due to their extensive range of applications as anticancer and antioxidants agents. Depending on the numerous biological reputations of these scaffolds, we explored the newly synthesized thiophene derivatives as a privileged structure for their antioxidant activity and ABTS antioxidant assay is used for this assessment.[39] The ABTS (2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)) examine is a typical method to assessment the overall antioxidant capacity of tissue, biological fluids, cell, natural and synthetic scaffolds. The estimate measures ABTS•+ radical cation consistence stimulated by MnO_2 which has green color and the resulted absorbance can be estimated at 734 nm. Antioxidants have the ability to reduce radical cation to ABTS by electron donation radical scavenging, so prevent the development of the green ABTS radical. ABTS antioxidant assay is fast and precise. However, the authors must conscious that chemical antioxidant assay may be disagreement with in vivo actions. The obtained results of

the ABTS antioxidant assay (Table 1) indicated that clubbing between thiophene and thiazole in compound **18c** promoted the antioxidant activity to the 84.26% percent inhibition that is very close to the reference antioxidant L-Ascorbic acid (88.44%). The combination between nicotinonitrile and thiophene moieties in the sulfide compound 27 promoted acceptable antioxidant activity with percent inhibition = 79.08%. The dithien-2-yl ketone compounds **20a** and **20c** displayed acceptable antioxidant activity with percent inhibition ranged 65.54% and 69.92%, respectively. Furthermore, compounds **5**, **13**, **18a**, **18b**, **25a** and **25c** exhibited a reasonable radical scavenging action with percent inhibition higher than 50%. .

TABLE 1 ABTS radical scavenging activity of the synthesized thien-2-yl heterocycles.

Compounds	Absorbance of samples	% Inhibition
Control of ABTS	0.502	0
Ascorbic-acid	0.058	88.44%
3a	0.269	46.41%
3b	0.302	39.84%
5	0.246	51.00%
7	0.267	46.81%
9	0.31	38.25%
11a	0.367	26.89%
11b	0.323	35.66%
13	0.196	60.96%
15	0.343	31.67%
18a	0.221	55.98%
18b	0.236	52.99%
18c	0.079	84.26%
20a	0.173	65.54%
20b	0.292	41.83%
20c	0.151	69.92%
25a	0.208	58.57%
25b	0.253	49.60%
25c	0.219	56.37%
27	0.105	79.08%
28	0.338	32.67%

3 | CONCLUSION

The present study proposals fast and effective method to the annulated heterocyclization using bi-nucleophiles. The precursor 5-bromo-2-(bromoacetyl)-thiophene was utilized as a vital intermediate in the synthetic tactic of novel annulated heterocycles via the reaction of with bi-nucleophiles as a route to higher heterocyclic systems substituted with 2-thienyl moiety, such as imidazo-thiazole, imidazo-tetrazole, imidazo-triazole, imidazo-pyridine, imidazo-imidazole, and quinoxaline. Moreover, the reaction of 5-bromo-2-(bromoacetyl)-thiophene with various thiocarbamoyl derivatives furnished a new series of thienyl-thiazoles and dithien-2-yl ketones based on the reaction conditions. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass analyses and were investigated for their antioxidant activity in vitro using ABTS assay. Among the tested thiophene-based compounds, compounds **18c** and **27** displayed the best antioxidant potentiality.

4 | EXPERIMENTAL

All melting points were determined on a Gallenkamp electric melting point apparatus. Infrared spectra were measured Thermo Scientific Nicolet iS10 FTIR spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data were obtained in DMSO-d_6 solution on JEOL's NMR spectrometer using TMS as internal reference. Mass spectra were recorded on a GC–MS QP-1000 EX Shimadzu instrument by electron ionization technique at 70 eV. Elemental analyses (C, H and N) were determined on Perkin-Elmer 2400 analyzer.

4.1 | General procedure of the synthesis of nitrogen containing heterocycles bearing thiophene moiety 3, 5, 7, 9, 11, 13 and 15:

A mixture of 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (**1**) (0.85 g, 0.003 mol) and 2-aminobenzothiazole derivatives **2**, 2-aminothiazole (**4**), 2-aminotetrazole (**6**), 2-aminotriazole (**8**), 2-aminopyridine derivatives **10**, 2-aminobenzimidazole (**15**) and/or *o*-phenylenediamine (**17**) (0.003 mol) was refluxed in absolute ethanol (25 mL) for 12 hours, the mixture was cooled. The formed products were collected and then recrystallized from ethanol/DMF mixture (5:1) to give compounds **3**, **5**, **7**, **9**, **11**, **13** and **15** respectively.

3-(5-Bromothiophen-2-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (3a): Yield = 54% (gray crystals); m.p. = 220-221°C. IR (KBr): 1604 (C=N), 1518 (C=C), 1273 (C-N), 635 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 8.69 (s, 1H, imidazole-H), 8.03 (d, *J* = 8.00 Hz, 1H, Ar-H),

7.96 (d, *J* = 8.00 Hz, 1H, Ar-H), 7.55 (t, *J* = 7.25 Hz, 1H, Ar-H), 7.42 (t, *J* = 7.25 Hz, 1H, Ar-H), 7.21-7.24 ppm (2d, *J* = 3.75 Hz, 2H, thiophene-H3 and -H4). ^{13}C NMR (DMSO-d_6): δ = 147.09, 140.27, 139.26, 131.29, 129.22, 126.80, 125.41, 125.10, 122.85, 113.47, 113.11, 109.66, 108.63 ppm. MS: *m/z* (%) = 336 (M^+, ^{81}Br, 19.24), 334 (M^+, ^{79}Br, 21.37), 290 (42.57), 258 (100), 217 (43.47), 152 (31.96), 126 (53.03), 105 (32.07). Analysis of $C_{13}H_7BrN_2S_2$ (335.24): Calculated: C, 46.58; H, 2.10; N, 8.36%. Found: C, 46.76; H, 2.04; N, 8.26%.

3-(5-Bromothiophen-2-yl)-7-methoxybenzo[*d*]imidazo[2,1-*b*]thiazole (3b): Yield = 48% (brown crystals); m.p. = 152-153°C. IR (KBr): 3434 (N-H), 2832 (CH_3), 1599 (C=N), 1524 (C=C), 1027 (C-O), 737 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 8.60 (s, 1H, imidazole-H), 7.88 (d, *J* = 9.00 Hz, 1H, Ar-H), 7.67 (d, *J* = 2.50 Hz, 1H, Ar-H), 7.18-7.20 (2d, *J* = 4.00 Hz, 2H, thiophene-H3 and -H4), 7.12, 7.14 (dd, *J* = 9.00, 2.50 Hz, 1H, Ar-H), 3.81 ppm (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 55.72, 108.62, 109.42, 113.97, 114.12, 122.70, 125.66, 130.57, 131.25, 137.36, 139.15, 139.55, 146.48, 157.11 ppm. MS: *m/z* (%) = 366 (M^+, ^{81}Br, 7.85), 348 (55.46), 248 (53.20), 160 (21.04), 113 (70.93), 69 (93.04), 43 (100). Analysis of $C_{14}H_9BrN_2OS_2$ (365.26): Calculated: C, 46.04; H, 2.48; N, 7.67%. Found: C, 46.25; H, 2.55; N, 7.56%.

5-(5-Bromothiophen-2-yl)imidazo[2,1-*b*]thiazole (5): Yield = 60% (brown crystals); m.p. = 181-182°C. IR (KBr): 1667 (C=N), 1634 (C=C), 1235 (C-N), 714 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 9.54 (s, 1H, imidazole-H), 7.95 (d, *J* = 4.00 Hz, 1H), 7.53 (d, *J* = 4.00 Hz, 1H), 7.33 (d, *J* = 4.00 Hz, 1H), 7.04 ppm (d, *J* = 4.00 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ = 183.04, 169.10, 141.42, 135.48, 132.71, 130.55, 123.01, 107.38, 54.19 ppm. MS: *m/z* (%) = 286 (M^+, ^{81}Br, 36.12), 284 (M^+, ^{79}Br, 38.33), 279 (59.01), 233 (82.58), 186 (76.06), 128 (100), 120 (65.07), 56 (61.12). Analysis of $C_9H_5BrN_2S_2$ (285.18): Calculated: C, 37.91; H, 1.77; N, 9.82%. Found: C, 37.80; H, 1.83; N, 9.91%.

6-(5-Bromothiophen-2-yl)-4*H*-imidazo[1,2-*d*]tetrazole (7): Yield = 50% (light brown crystals); m.p. = 212-213°C. IR (KBr): 3325 (N-H), 1663 (C=N), 1590 (C=C), 1340 (C-N), 687 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 7.98 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.51 (d, *J* = 4.00 Hz, 1H, thiophene-H), 6.76 (s, 1H, NH), 5.78 ppm (s, 1H, imidazole-H). ^{13}C NMR (DMSO-d_6): δ = 156.51, 141.81, 135.36 (2C), 132.70 (2C), 122.96 ppm. MS: *m/z* (%) = 271

(M^+, ^{81}Br, 13.37), 269 (M^+, ^{79}Br, 16.56), 219 (48.16), 206 (62.33), 154 (51.37), 98 (57.90), 84 (77.80), 43 (100). Analysis of $C_7H_4BrN_5S$ (270.11): Calculated: C, 31.13; H, 1.49; N, 25.93%. Found: C, 30.96; H, 1.43; N, 25.81%.

6-(5-Bromothiophen-2-yl)-4*H*-imidazo[1,2-*b*][1,2,4]triazole (9): Yield = 37% (pale brown crystals); m.p. = 262-263°C. IR (KBr): 3213 (N-H), 1665 (C=N), 1575 (C=C), 747 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 8.46 (s, 1H, triazole-H), 8.01 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.55 (d, *J* = 4.00 Hz, 1H, thiophene-H), 5.81 (s, 1H, imidazole-H), 5.68 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 150.75, 141.22, 140.87, 135.83, 135.55, 132.83 (2C), 123.34 ppm. MS: *m/z* (%) = 270 (M^+, ^{81}Br, 10.88,), 268 (M^+, ^{79}Br, 12.36), 152 (44.33), 141 (60.96), 119 (28.75), 84 (49.24), 77 (100), 42 (44.49). Analysis of $C_8H_5BrN_4S$ (269.12): Calculated: C, 35.70; H, 1.87; N, 20.82%. Found: C, 35.51; H, 1.95; N, 20.90%.

2-(5-Bromothiophen-2-yl)-6-chloroimidazo[1,2-*a*]pyridine (11a): Yield = 39% (gray crystals); m.p. = 240-241°C. IR (KBr): 1646 (C=N), 1594 (C=C), 1251 (C-N), 800 (C-Cl), 706 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 9.06 (s, 1H, pyridine-H), 8.52 (s, 1H, imidazole-H), 7.81 (d, *J* = 9.00 Hz, 1H, pyridine-H), 7.74 (d, *J* = 9.00 Hz, 1H, pyridine-H), 7.54 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.33 ppm (d, *J* = 4.00 Hz, 1H, thiophene-H). ^{13}C NMR (DMSO-d_6): δ = 143.24, 137.10, 131.68, 131.46, 127.46, 125.85, 125.67, 122.70, 121.02, 117.58, 109.82 ppm. MS: *m/z* (%) = 314 (M^+, ^{81}Br, 90.88), 312 (M^+, ^{79}Br, 100), 311 (84.23), 309 (42.68), 77 (2.19), 43 (29.45). Analysis of $C_{11}H_6BrClN_2S$ (313.60): Calculated: C, 42.13; H, 1.93; N, 8.93%. Found: C, 42.35; H, 2.05; N, 8.79%.

2-(5-Bromothiophen-2-yl)imidazo[1,2-*a*]pyridine (11b): Yield = 46% (white crystals); m.p. = 213-214^{o}C. IR (KBr): 1651 (C=N), 1607 (C=C), 1361 (C-N), 620 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 8.78 (d, *J* = 6.50 Hz, 1H, pyridine-H), 8.64 (s, 1H, imidazole-H), 7.87-7.80 (m, 2H, pyridine-H), 7.57 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.40 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.37 ppm (d, *J* = 6.50 Hz, 1H, pyridine-H). ^{13}C NMR (DMSO-d_6): δ = 140.45, 132.92, 131.98, 130.84, 130.18, 128.85, 128.48, 116.95, 114.95, 112.48, 110.77 ppm. MS: *m/z* (%) = 280 (23.04, M^+ + 2), 278 (26.04, M^+), 167 (68.96), 82 (100), 90 (85.88), 92 (96.02), 139 (82.95), 178 (95.22). Analysis of $C_{11}H_7BrN_2S$ (279.16): Calculated: C, 47.33; H, 2.53; N, 10.04%. Found: C, 47.44; H, 2.55; N, 10.11%.

3-(5-Bromothiophen-2-yl)-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole (13): Yield = 55% (gray crystals); m.p. = 242-243°C. IR (KBr): 3237 (N-H), 1676 (C=N), 1524 (C=C), 1200 (C-N), 671 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 8.17 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.81 (d, *J* = 7.50 Hz, 1H, Ar-H), 7.57 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.56 (s, 1H, NH), 7.32 (t, *J* = 7.50 Hz, 1H, Ar-H), 7.26 (t, *J* = 7.50 Hz, 1H, Ar-H), 7.19-7.17 (m, 1H, Ar-H), 5.88 ppm (s, 1H, imidazole-H). ^{13}C NMR (DMSO-d_6): δ = 142.01, 135.85, 135.74, 132.81, 131.19, 123.90, 123.21, 122.69, 121.11, 111.66, 110.99, 109.17, 103.45 ppm. MS: *m/z* (%) = 319 (M^+, ^{81}Br, 33.23), 317 (M^+, ^{79}Br, 29.91), 219 (54.68), 119 (45.68), 75 (6.38). Analysis of $C_{13}H_8BrN_3S$ (318.19): Calculated: C, 49.07; H, 2.53; N, 13.21%. Found: C, 49.28; H, 2.41; N, 13.07%.

2-(5-Bromothiophen-2-yl)quinoxaline (15): Yield = 68% (brown crystals); m.p. = 168-169°C. IR (KBr): 1639 (C=N), 1546 (C=C), 1309 (C-N), 610 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 9.52 (s, 1H, pyrazine-H), 8.06 (d, *J* = 3.50 Hz, 1H, thiophene-H), 8.04 (d, *J* = 1.50 Hz, 1H, Ar-H), 7.99-7.97 (dd, *J* = 8.25, 1.50 Hz, 1H, Ar-H), 7.84-7.76 (m, 2H, Ar-H), 7.40 ppm (d, *J* = 3.50 Hz, 1H, thiophene-H). ^{13}C NMR (DMSO-d_6): δ = 146.20, 143.55, 142.21, 140.99, 140.84, 132.36, 130.95, 129.75, 129.38, 12.96, 128.48, 117.01 ppm. MS: *m/z* (%) = 292 (M^+, ^{81}Br, 9.76), 290 (M^+, ^{79}Br, 13.35), 266 (30.99), 127 (41.74), 105 (55.15), 91 (100), 77 (70.39), 62 (57.38). Analysis of $C_{12}H_7BrN_2S$ (291.17): Calculated: C, 49.50; H, 2.42; N, 9.62%. Found: C, 49.38; H, 2.45; N, 9.70%.

4.2 | Synthesis of 4-(5-bromothiophen-2-yl)-3-phenylthiazol-2(3*H*)-ylidene derivatives 18a-c:

A mixture of each activated nitrile derivative **16a**, **16b** or **16c** (0.002 mol), phenyl isothiocyanate (0.24 mL, 0.002 mol) and potassium hydroxide (0.12 g, 0.002 mol) was stirred in 15 mL DMF for overnight. Then 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (**1**) (0.57 g, 0.002 mol) was added with continuous stirring for additional 4 hours. The suspension was poured into ice water and the solid product that obtained was collected by filtration and recrystallized from ethanol to give **18a, 18b** and **18c**, respectively.

2-(4-(5-Bromothiophen-2-yl)-3-phenylthiazol-2(3*H*)-ylidene)-malononitrile (18a): Yield = 52% (yellow powder); m.p. = 216-217°C. IR (KBr): 2214, 2198 (C≡N), 1598 (C=C), 696 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 7.44-7.43 (m, 5H, Ar-H), 7.38 (s, *J* = 4.00 Hz, 1H, thiophene-H), 7.25 ppm (d, *J* = 4.00 Hz, 2H, thiophene-H and thiazole-H). ^{13}C NMR (DMSO-

d_6): δ = 173.17, 164.71, 158.8,4 147.21, 139.52, 131.72, 129.66 (2C), 129.34, 125.96, 122.18 (2C), 118.01, 113.27, 91.56, 79.86 ppm. MS: *m/z* (%) = 387 (M^+, ^{81}Br, 49.16), 385 (M^+, ^{79}Br, 53.57), 322 (97.24), 320 (100), 271 (80.08), 137 (80.75), 108 (56.65), 63 (93.65). Analysis of $C_{16}H_8BrN_3S_2$ (386.29): Calculated: C, 49.75; H, 2.09; N, 10.88%. Found: C, 49.61; H, 2.16; N, 10.76%.

Ethyl 2-(4-(5-bromothiophen-2-yl)-3-phenylthiazol-2(3*H*)-ylidene)-2-cyanoacetate (18b): Yield = 82% (yellowish white powder); m.p. = 177-178°C. IR (KBr): 2981 (C-H), 2205 (C≡N), 1692 (C=O), 693 cm^{-1} (C-Br). ^{1}H NMR ($CDCl_3$): δ = 7.64-7.59 (m, 1H, Ar-H), 7.51 (t, *J* = 8.50 Hz, 2H, Ar-H), 7.33 (d, *J* = 9.50 Hz, 2H, Ar-H), 6.82 (s, 1H, thiazole-H), 6.81 (d, *J* = 4.00 Hz, 1H, thiophene-H), 6.46 (d, *J* = 4.00 Hz, 1H, thiophene-H), 4.24 (q, *J* = 7.25 Hz, 2H, CH_2), 1.26 ppm (t, *J* = 7.25 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 168.01, 167.58, 135.74, 133.58, 131.91 (2C), 130.06, 129.83 (2C), 129.27, 126.28, 125.81, 115.48, 114.78, 109.57, 97.07, 61.12, 14.31 ppm. MS: *m/z* (%) = 434 (M^+, ^{81}Br, 15.36), 432 (M^+, ^{79}Br, 17.38), 200 (53.27), 189 (73.00), 133 (89.79), 91 (100), 78 (86.49), 64 (63.55). Analysis of $C_{18}H_{13}BrN_2O_2S_2$ (433.34): Calculated: C, 49.89; H, 3.02; N, 6.46%. Found: C, 49.70; H, 3.11; N, 6.31%.

2-(4-(5-Bromothiophen-2-yl)-3-phenylthiazol-2(3*H*)-ylidene)-2-cyanoacetamide (18c): Yield 57 % (orang crystal); m.p. = 182-183°C; IR (KBr): 3396, 3314 (NH_2), 2184 (C≡N), 1641 (C=O), 696 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 7.57 (s, 2H, NH_2), 7.52-7.47 (m, 5H, Ar-H), 7.35 (s, 1H, thiazole-H), 7.07 (d, *J* = 3.50 Hz, 1H, thiophene-H), 6.80 ppm (d, *J* = 3.50 Hz, 1H, thiophene-H). ^{13}C NMR (DMSO-d_6): δ = 167.69, 165.57, 136.00 133.94, 131.55, 131.30, 130.37 (2C), 130.27, 129.95, 129.48 (2C), 116.29, 113.92, 110.83, 66.45 ppm. MS: *m/z* (%) = 405 (M^+, ^{81}Br, 6.33), 158 (51.27), 117 (86.89), 86 (53.83), 80 (97.52), 77 (100), 51 (20.85). Analysis of $C_{16}H_{10}BrN_3OS_2$ (404.30): Calculated: C, 47.53; H, 2.49; N, 10.39%. Found: C, 47.38; H, 2.56; N, 10.48%.

4.3 | Synthesis of 4-amino-5-(5-bromothiophene-2-carbonyl)-2-(phenylamino)thiophene derivatives 20a-c:

A mixture of 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (**1**) (0.28 g, 0.001 mol) and each derivative of cyano-3-mercapto-3-(phenylamino)acrylates **19** (0.001 mol) was refluxed in absolute ethanol (15 mL) and triethylamine (0.5 mL) for 2 hours. The reaction mixture was

permitted to cool and then the formed solid product was collected and recrystallized from EtOH/DMF mixture (5:1) to give the corresponding 4-aminothiophene derivatives **20a**, **20b** and **20c**.

4-Amino-5-(5-bromothiophene-2-carbonyl)-2-(phenylamino)thiophene-3-carbonitrile (20a): Yield = 43% (brown powder); m.p. = 122-123°C. IR (KBr): (NH_2), 4357, 3380, 3234 (NH_2 and NH), 2216 (C≡N), 1609 (conjugated C=O), 690 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 10.72 (s, 1H, NH), 8.15 (s, 2H, NH_2), 7.45-7.43 (m, 4H, Ar-H), 7.38 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.26-7-22 ppm (m, 2H, Ar-H and thiophene-H). ^{13}C NMR (DMSO-d_6): δ = 173.18, 164.74, 158.86, 147.21, 139.52, 131.76, 129.68 (2C), 129.38, 125.99, 122.20 (2C), 118.03, 113.28, 91.55, 79.84 ppm. MS: *m/z* (%) = 405 (M^+, ^{81}Br, 18.76), 403 (M^+, ^{79}Br, 20.94), 371 (39.59), 272 (43.39), 115 (11.94), 81 (46.74), 41 (100). Analysis of $C_{16}H_{10}BrN_3OS_2$ (404.30): Calculated: C, 47.53; H, 2.49; N, 10.39%. Found: C, 47.44; H, 2.46; N, 10.45%.

Ethyl-4-amino-5-(5-bromothiophene-2-carbonyl)-2-(phenylamino)thiophene-3-carboxylate (20b): Yield = 70% (orang crystal); m.p. = 162-163°C. IR (KBr): 3473, 3272 (NH_2 and NH), 1659 (C=O), 742 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 10.27 (s, 2H, NH_2), 9.09 (s, 12H, NH_2), 7.50-7.44 (m, 4H, Ar-H), 7.33 (d, *J* = 4.0 Hz, 1H, thiophene-H), 7.31-7.27 (m, 1H, Ar-H), 7.22 (d, *J* = 4.00 Hz, 1H, thiophene-H), 4.36 (q, *J* = 7.25 Hz, 2H, CH_2) 1.34 ppm (t, *J* = 7.25 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 172.79, 164.91, 163.99, 158.57, 147.74, 138.86, 131.30, 129.50 (2C), 128.57, 126.07, 122.49 (2C), 117.15, 96.34, 91.26, 60.36, 14.09 ppm. MS: *m/z* (%) = 452 (M^+, ^{81}Br, 19.35), 450 (M^+, 79Br, 22.40), 320 (100), 297 (52.95), 127 (61.12), 104 (80.14), 75 (57.78). Analysis of $C_{18}H_{15}BrN_2O_3S_2$ (451.35): Calculated: C, 47.90; H, 3.35; N, 6.21%. Found: C, 47.74; H, 3.42; N, 6.33%.

4-Amino-5-(5-bromothiophene-2-carbonyl)-2-(phenylamino)thiophene-3-carboxamide (**20c**): Yield = 49% (Light brown powder); m.p. = 280-281°C. IR (KBr): 3454, 3404, 3330, 3256 (NH_2 and NH), 1653 (C=O), 691 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 10.26 (s, 1H, NH), 8.08 (s, 2H, NH_2), 7.49 (s, 2H, NH_2), 7.42-7.37 (m, 5H, Ar-H and thiophene-H), 7.26 (d, *J* = 4.50 Hz, 1H, thiophene-H), 7.17-7.14 ppm (m, 1H, Ar-H). ^{13}C NMR (DMSO-d_6): δ = 173.08, 165.97, 160.55, 158.48, 148.05, 140.23, 131.62, 129.54 (2C), 128.98, 124.56, 120.72 (2C), 117.44, 103.66, 92.89 ppm. MS: *m/z* (%) = 423 (M^+, ^{81}Br, 42.27), 421 (M^+, ^{79}Br, 45.49),

407 (50.61), 387 (59.38), 368 (54.19), 271 (59.15), 255 (100), 95 (52.03). Analysis of $C_{16}H_{12}BrN_3O_2S_2$ (422.32): Calculated: C, 45.51; H, 2.86; N, 9.95%. Found: C, 45.67; H, 2.78; N, 9.86%.

4.4 | Synthesis of 4-amino-5-(5-bromothiophene-2-carbonyl)-*N*-phenyl-2-(phenylamino)-thiophene-3-carboxamide derivatives 25a-c:

A suspension of 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (**1**) (0.28 g, 0.001 mol) and each *N*-aryl-2-cyano-3-mercapto-3-(phenylamino)-acrylamide derivative **24a**, **24b** or **24c** (0.001 mol) was refluxed for 45 minutes in absolute ethanol (15 mL) and triethylamine (0.5 mL), then allowed to cool. The formed solid product was collected and recrystallized from ethanol/DMF mixture (5:1) to give **25a**, **25b** and **25c**.

4-Amino-5-(5-bromothiophene-2-carbonyl)-*N*-phenyl-2-(phenylamino)thiophene-3-carboxamide (25a): Yield = 47% (yellow crystals); m.p. = 225-226°C. IR (KBr): 3369, 3339, 3274 (NH_2 and NH), 1637 (C=O), 681 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 9.98 (s, 1H, NH), 9.97 (s, 1H, NH), 7.99 (s, 2H, NH_2), 7.43 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.41-7.29 (m, 8H, Ar-H), 7.27 (d, 1H, *J* = 4.00 Hz, 1H, thiophene-H), 7.16-7.14 (m, 1H, Ar-H), 7.07-7.05 ppm (m, 1H, Ar-H). ^{13}C NMR (DMSO-d_6): δ = 173.01, 162.09, 159.47, 158.31, 148.05, 140.47, 138.87, 131.62, 129.44 (2C), 128.97, 128.39 (2C), 124.54, 123.47, 120.90 (2C), 120.33 (2C), 117.89, 105.11, 92.84 ppm. MS: *m/z* (%) = 499 (M^+, ^{81}Br, 15.69), 497 (M^+, ^{79}Br, 14.93), 437 (67.68), 394 (64.20), 352 (63.71), 162 (66.06), 153 (100). Analysis of $C_{22}H_{16}BrN_3O_2S_2$ (498.41): Calculated: C, 53.02; H, 3.24; N, 8.43%. Found: C, 53.11; H, 3.10; N, 8.51%.

4-Amino-5-(5-bromothiophene-2-carbonyl)-2-(phenylamino)-*N*-(*p*-tolyl)thiophene-3-carboxamide (25b): Yield = 70% (yellow crystals); m.p. = 220-221°C; IR (KBr): 3383, 3330, 3289 (NH_2 and NH), 2916 (C-H), 1632 (C=O), 679 cm^{-1} (C-Br). ^{1}H NMR (DMSO-d_6): δ = 9.98 (s, 1H, NH), 9.81 (s, 1H, NH), 8.04 (s, 2H, NH_2), 7.42 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.39-7.37 (m, 6H, Ar-H), 7.32 (d, *J* = 9.00 Hz, 2H, Ar-H), 7.25 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.15-7.12 (m, 1H, Ar-H), 2.34 ppm (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 173.00, 161.92, 159.32, 158.34, 148.07, 140.53, 136.33, 132.45, 131.76, 129.46 (2C), 129.00, 128.80 (2C), 124.49, 120.84 (2C), 120.36 (2C), 117.50, 97.06, 104.73, 20.51 ppm. MS: *m/z* (%) = 513 (M^+, ^{81}Br, 9.94), 511 (M^+, ^{79}Br, 11.11), 422 (42.52), 347 (66.78), 297 (52.49), 112

(54.59), 71 (75.55), 57 (100). Analysis of $C_{23}H_{18}BrN_3O_2S_2$ (512.44): Calculated: C, 53.91; H, 3.54; N, 8.20%. Found: C, 53.75; H, 3.62; N, 8.06%.

4-Amino-5-(5-bromothiophene-2-carbonyl)-*N*-(4-methoxyphenyl)-2-(phenylamino)-thiophene-3-carboxamide (25c): Yield = 51% (yellow crystals); m.p. = 205-206°C. IR (KBr): 3384, 3326 (NH_2 and NH), 1629 (C=O), 682 cm^{-1} (C-Br). ^1H NMR (DMSO-d_6): δ = 9.97 (s, 1H, NH), 9.83 (s, 1H, NH), 7.98 (s, 2H, NH_2), 7.54 (d, *J* = 9.00 Hz, 2H, Ar-H), 7.42 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.40-7.39 (m, 4H, Ar-H), 7.26 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.15-7.12 (m, 1H, Ar-H), 6.89 (d, *J* = 9.00 Hz, 2H, Ar-H), 3.71 ppm (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ = 173.02, 161.77, 159.17, 158.35, 155.54, 148.11, 140.54, 131.89, 131.69, 129.49 (2C), 129.03, 124.48, 122.01 (2C), 120.80 (2C), 117.52, 113.58 (2C), 105.25, 92.89, 55.22 ppm. MS: *m/z* (%) = 529 (M^+, ^{81}Br, 16.34), 527 (M^+, ^{79}Br, 19.67), 493 (53.71), 335 (74.43), 248 (72.89), 112 (59.48), 76 (60.87), 55 (100). Analysis of $C_{23}H_{18}BrN_3O_3S_2$ (528.44): Calculated: C, 52.28; H, 3.43; N, 7.95%. Found: C, 52.21; H, 3.47; N, 8.01%.

4.5 | Synthesis of 2-((2-(5-bromothiophen-2-yl)-2-oxoethyl)thio)-4,6-dimethyl-nicotinonitrile (27):

To a mixture of 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (**1**) (1.13 g, 0.004 mol) and 2-mercapto-4,6-dimethylbenzonitrile (**26**) (0.59 g, 0.004 mol) in 20 mL acetone, potassium carbonate (0.55 g, 0.004 mol) was added and then refluxed for 3 hours. The reaction mixture was decanted onto crushed ice and when the precipitated product was formed, it was collected by the filtration and then washed with water. The obtained solid was recrystallized from ethanol to give the corresponding sulfide **27.**

Yield = 68% (yellow crystals); m.p. = 142-143°C. IR (KBr): 2914 (C-H), 2214 (C≡N), 1658 (C=O), 707 cm^{-1} (C-Br). ^1H NMR ($CDCl_3$): δ = 7.66 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.14 (d, *J* = 4.00 Hz, 1H, thiophene-H), 6.77 (s, 1H, pyridine-H), 4.45 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.28 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 185.56, 161.18, 159.85, 152.22, 144.47, 132.55, 131.22, 123.09, 120.37, 114.74, 104.61, 36.49, 24.17, 20.06 ppm. MS: *m/z* (%) = 368 (M^+, ^{81}Br, 48.24), 366 (M^+, ^{79}Br, 44.37), 355 (96.42), 206 (64.76), 160 (42.14), 132 (65.53), 125 (100), 47 (72.14). Analysis of $C_{14}H_{11}BrN_2OS_2$ (367.28): Calculated: C, 45.78; H, 3.02; N, 7.63%. Found: C, 45.91; H, 3.07; N, 7.71%.

4.6 | Synthesis of (3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)(5-bromothiophen-2-yl)methanone (28):

A solution of sulfide compound **27** (0.36 g, 0.001 mol) was refluxed for 2 hours in sodium ethoxide, which prepared from 0.11 g Na and 20 mL absolute ethanol. The mixture was permitted to be cool and then poured onto ice-water. The obtained product was dried out and recrystallized from ethanol to give **28**.

Yield = 56% (orange crystals); m.p. = 188-189°C. IR (KBr): 3491 3276 (NH_2), 1590 (conjugated C=O), 736 cm^{-1} (C-Br). ^1H NMR ($CDCl_3$): δ = 7.73 (d, *J* = 4.00 Hz, 1H, thiophene-H), 7.41 (broad s, 2H, NH_2), 7.12 (d, *J* = 4.00 Hz, 1H, thiophene-H), 6.92 (s, 1H, pyridine-H), 2.77 (s, 3H, CH_3), 2.63 ppm (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ = 177.14, 159.28, 152.64, 146.44, 145.71, 130.21, 129.61, 121.49, 121.10, 119.12, 100.67, 22.78, 19.65 ppm. MS: *m/z* (%) = 368 (84.88, M^+ + 2), 366 (85.98 M^+) 328 (44.85), 191 (67.24), 118 (100), 112 (81.74), 42 (90.80). Analysis of $C_{14}H_{11}BrN_2OS_2$ (367.28): Calculated: C, 45.78; H, 3.02; N, 7.63%. Found: C, 45.66; H, 3.08; N, 7.71%.

4.7 | ABTS antioxidant assay:

The radical cation derived from ABTS was prepared by addition of 2 mL ABTS solution (60 μM) to 3 mL MnO_2 (25 mg/mL) in 5 mL aqueous buffer solution (pH = 7). The produced suspension was shaken for a few minutes, centrifuged and then filtered. The absorbance (A control) of the green-blue solution that obtained (ABTS radical solution) was determined at λ_{max} 734 nm. The absorbance (A test) of each tested compound was measured upon the addition of (20 μL of 1 mg/mL) solution in spectroscopic grade MeOH/phosphate buffer (1:1) to the ABTS solution. The decrease in the absorbance is expressed as % inhibition, which is calculated from the equation: %Inhibition = [A(control) – A(test) / A(control)] × 100

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