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Synthesis, reactions and biological evaluation of some novel thienothiophene derivatives

Mounir Abbas Ali Mohamed *, Hanan Salah and Ahmed Mohamed Mohamed El-Saghier

Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt
mounir_abbas@yahoo.com (M.A.A.M.), hanansalah7396@gmail.com (H.S.), el_saghier@yahoo.com (A.M.M.E.)

* *Corresponding author at: Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt.*
Tel: +20.1.016395449 Fax: +20.093.4601159 e-mail: mounir_abbas@yahoo.com (M.A.A. Mohamed).

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ABSTRACT

Synthesis of some new *bis*(chalcones)-based thienothiophene derivatives and study of their synthetic utilities as building blocks for new *bis*(thiazole), *bis*(dihydropyran), *bis*(dihydro pyridine), *bis*(isoxazoles), *bis*(pyrazoles), *bis*(hydropyrimidinethiones), *bis*(tetrahydro diazepines, oxazepines) and *bis*(dihydrobenzodiazepnies, benzoxazepines) each linked to a thienothiophene core, is reported. Biological evaluation of the obtained compounds as antibacterial agents was achieved. Compounds 4b, 4c, 7a, 6a, 9a and 11b were found to be very potent against *P. aeruginosa, E. coli* and *K. pneumonia*.

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1. Introduction

Chalcones are very interesting molecules due to their diverse applications in different fields. They display a wide range of pharmacological properties, including antimutagenic and antitumor-promoting activities, antibacterial, anti-inflammatory, antiulcerative, and hepatoprotective activities [1-5]. Chalcones also are useful intermediates for the synthesis of five-, six- and seven-membered heterocyclic compounds [6-10]. In addition, considerable attention has been focused on thienothiophenes due to their interesting biological activities. They have been tested as potential antitumor, antiviral, antibiotic and antiglaucoma drugs or as inhibitors of platelet aggregation [11-15]. Recently, Mashraqui [16] had described the application of thieno[2,3-b]thiophene in the design of a novel nonlinear optics (NLO) system by incorporating this nucleus within an unsymmetrically functionalized cyclophane. Furthermore, attention has been increasingly paid in recent years to the synthesis of *bis*-heterocyclic for their numerous applications as electrical materials [17], chelating agents, and metal ligands [18]. They also exhibit various biological activities including antibacterial, fungicidal, tuberculostatic, antitumor and as antimicrobial [19-38] and plant growth regulative properties [39,40]. Moreover, compounds including *bis*-heterocyclic moieties were encountered in many bioactive natural product and recent reports showed that among libraries of derivatized heterocycles, the most active library compounds had a *bis*-heterocyclic structure [41-49].

2. Experimental

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using TMS as internal reference (Chemical shifts in δ, ppm), and IR spectra were obtained on a Nicolet 710 FT-IR spectrometer (KBr, ν, cm^{-1}).

2.1. Synthesis of 1,1'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)diethanone (1)

To a solution of anhydrous potassium carbonate (~5 g) in dry benzene (30 mL), acetylacetone 1.03 mL (0.01 mol), TBAB (~50 mg), carbon disulfide 0.9 mL (0.015 mol) was added drop-wise with continuous stirring. After 30 min the reaction mixture was cooled to 0 °C and then treated with chloro acetone (0.190 mL, 0.02 mol).

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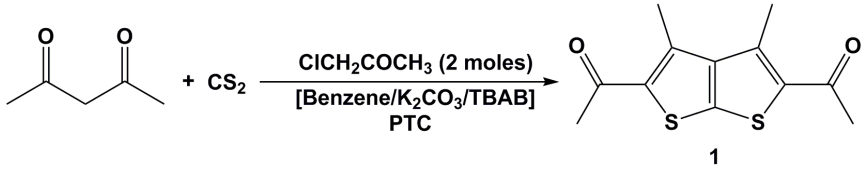
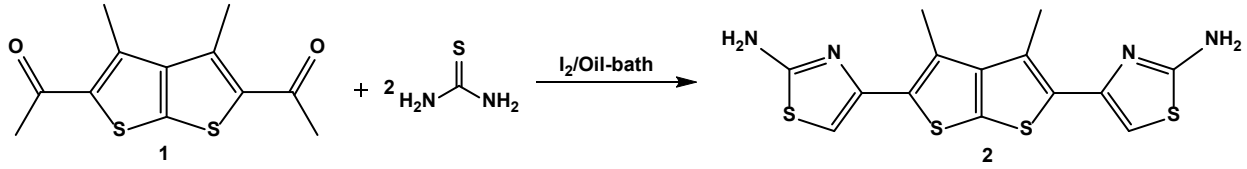
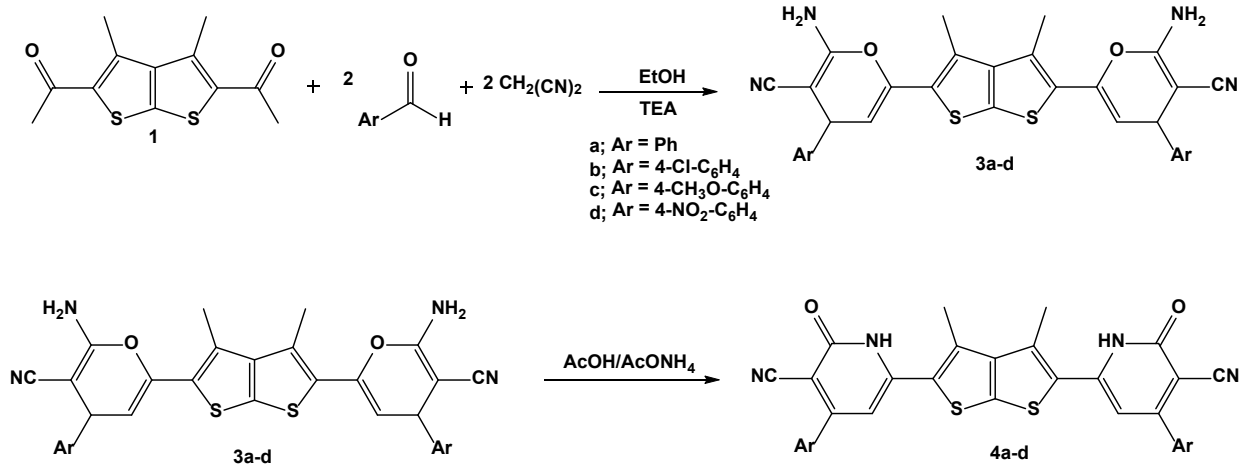


Scheme 1. Synthesis of 1,1'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)diethanone **1** under phase transfer catalysis conditions.



Scheme 2. Synthesis of 2,2'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)dithiazol-5-amine (**2**).



Scheme 3. Synthesis of 6,6'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)-*bis*(2-oxo-4-aryl-1,2-dihydropyridine-3-carbonitrile) derivatives (**4a-d**).

The reaction mixture was further stirred for 3 h, and then filtered off and benzene layer was washed thoroughly with water and dried over anhydrous magnesium sulphate and evaporated in vacuum to give compound **1** (Scheme 1). Color: Yellow. Yield: 92%. M.p.: 154-156 °C. Anal. calcd. for $C_{12}H_{12}O_2S_2$: C, 57.12; H, 4.79; S, 25.41. Found: C, 56.88; H, 4.50; S, 25.01%. FT-IR (KBr, ν, cm^{-1}): 1699 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.55 (s, 6H, $2COCH_3$), 2.81 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.3, 38.50, 131.7, 134.5, 143.4, 160.5, 191.2. MS (EI, *m/z* (%)): 252 (M^+, 12%), 250 (100%), 164 (34%), 134 (18%).

2.2. Synthesis of 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)dithiazol-2-amine (2)

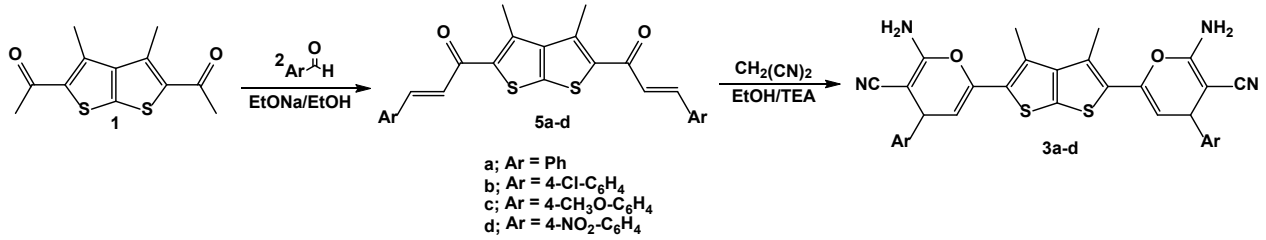
A mixture of compound **1** (2.52 g, 0.01 mol), thiourea (1.52 g, 0.02 mol) and iodine (2.54 g, 0.02 mol) was fused on oil bath at 100 °C for 3 h. The formed slurry was treated with water (25 mL) and boiled then was neutralized with ammonia solution (pH = 7) and the formed solid was collected by filtration and recrystallized from ethanol into white needles (Scheme 2). Color: White. Yield: 77%. M.p.: 264-266 °C, Lit. 295 °C [50,51]. Anal. calcd. for $C_{14}H_{12}N_4S_4$: C, 46.13; H, 3.32; N, 15.37. Found: C, 45.76; H, 3.05; N, 15.20%. FT-IR (KBr, ν, cm^{-1}): 3398, 3312 (NH_2). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 6.72 (s, 4H, $2NH_2$), 6.80-7.13 (dd, 2H, 2=CH). MS (EI, *m/z* (%)): 365 (M^{+1}, 10), 364 (M^+, 42), 331 (50), 207 (45), 79 (98).

2.3. Synthesis of 6,6'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-amino-4-aryl- 4H-pyran-3-carbonitrile) (3a-d)

A mixture of compound **1** (0.252 g, 0.001 mol), aromatic aldehyde (0.002 mol) and malononitrile (0.132 g, 0.002 mol) in absolute ethanol (25 mL) was treated with few drops of triethylamine as catalyst and then was heated under reflux for different periods of time (2-4 h). Solvent was removed under vacuum and the residual mass was triturated with light petroleum (40-60 °C). The formed solid was recrystallized from ethanol into compounds **3a-d** (Scheme 3).

6, 6'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(2-amino-4-phenyl-4H-pyran-3-carbonitrile) (**3a**): Color: Pale yellow. Yield: 67%. M.p.: 166-168 °C. FT-IR (KBr, ν, cm^{-1}): 3294, 3206 (NH_2), 2212 (CN). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 4.65 (d, *J* = 4.8 Hz, 2H, $2CH_{\gamma\text{-pyran}}$), 5.85 (d, *J* = 5.6 Hz, 2H, 2=CH), 6.87-6.98 (br, 4H, $2NH_2$), 7.23-7.45 (m, 10H, CH_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.03 ($2CH_3$), 67.08 ($CH_{\gamma\text{-pyran}}$), 113.18 (CN), 128.19, 136.02, 140.00, 143.65 (Thienothiophene ArC's), 129.16, 129.56, 144.78, 148.57 (pyran ArC's), 129.56, 130.49, 138.90, 139.49 (Ph ArC's). Anal. calcd. for $C_{32}H_{24}N_4O_2S_2$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.20; H, 4.36; N, 10.16%.

6, 6'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(2-amino-4-(4-chlorophenyl)-4H-pyran-3-carbonitrile) (**3b**): Color: White. Yield: 75%. M.p.: 144-146 °C. Anal. calcd. for $C_{32}H_{22}Cl_2N_4O_2S_2$: C, 61.05; H, 3.52; N, 8.90. Found: C, 60.15; H, 3.25; N, 8.70%.



Scheme 4. Synthesis of chalcone derivatives **5a**-**d**.

FT-IR (KBr, ν, cm^{-1}): 3312, 3232 (NH_2), 2209 (CN). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.60 (s, 6H, $2CH_3$), 4.75 (d, *J* = 4.8 Hz, 2H, $2CH_{\gamma\text{-pyran}}$), 5.80 (d, *J* = 5.6 Hz, 2H, 2=CH), 6.81-6.96 (br, 4H, $2NH_2$), 7.35-7.56 (m, 8H, CH_{arom}).

6,6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(2-amino-4-(4-methoxyphenyl)-4H-pyran-3-carbonitrile) (**3c**): Color: Yellow. Yield: 82%. M.p.: 176-178 °C. Anal. calcd. for $C_{34}H_{28}N_4O_4S_2$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.40, H, 4.25, N, 9.18%. FT-IR (KBr, ν, cm^{-1}): 3303, 3225 (NH_2), 2210 (CN). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 3.88 (s, 6H, $2OCH_3$), 4.66 (d, *J* = 4.6 Hz, 2H, $2CH_{\gamma\text{-pyran}}$), 5.65 (d, *J* = 5.6 Hz, 2H, 2=CH), 6.88-7.06 (br, 4H, $2NH_2$), 7.32-7.50 (m, 8H, CH_{arom}).

6,6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(2-amino-4-(4-nitrophenyl)-4H-pyran-3-carbonitrile) (**3d**): Color: Brown. Yield: 77%. M.p.: 156-158 °C. Anal. calcd. for $C_{32}H_{22}N_6O_6S_2$: C, 59.07; H, 3.41; N, 12.92. Found: C, 58.72; H, 3.01; N, 12.66%. FT-IR (KBr, ν, cm^{-1}): 3315, 3238 (NH_2), 2213 (CN). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 4.60 (d, *J* = 4.8 Hz, 2H, $2CH_{\gamma\text{-pyran}}$), 5.68 (d, *J* = 5.8 Hz 2H, 2=CH), 6.78-6.86 (br, 4H, $2NH_2$), 7.33-7.55 (m, 8H, CH_{arom}).

2.4. Synthesis of 6,6′-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(4-aryl-2-oxo-1,2-dihydropyridine-3-carbonitrile) (4a-d)

Compound **3a**-**d** (0.001 mol) was dissolved in glacial acetic acid (20 mL) and then was treated with ammonium acetate (0.12 g, 0.0015 mol). The reaction mixture was heated under reflux for 3 h. Solvent was removed under vacuum; ice-cold water was then added to the residual mass and left overnight. The formed soled was filtered off and recrystallized from ethanol to give compound **4a**-**d** (Scheme 3).

6,6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2,5-diyl)bis(2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile) (**4a**): Color: Yellow. Yield: 68%. M.p.: 138-140 °C. Anal. calcd. for $C_{32}H_{20}N_4O_2S_2$: C, 69.05; H, 3.62; N, 10.07. Found: C, 68.66; H, 3.22; N, 9.78%. FT-IR (KBr, ν, cm^{-1}): 3234 (NH), 2210 (CN), 1688 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 5.58 (s, 2H, $2CH_{olefenic}$), 7.33-7.55 (m, 10H, CH_{arom}), 12.03 (br, 2H, 2NH).

6,6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile) (**4b**): Color: Pale yellow. Yield: 72 %. M.p.: 155-157 °C. Anal. calcd. for $C_{32}H_{18}Cl_2N_4O_2S_2$: C, 61.44; H, 2.90; N, 8.96. Found: C, 61.02; H, 2.65; N, 8.68%. FT-IR (KBr, ν, cm^{-1}): 3224 (NH), 2214 (CN), 1698 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 5.62 (s, 2H, $2CH_{olefenic}$), 7.30-7.52 (m, 8H, CH_{arom}), 9.22 (s, 2H, 2NH).

6,6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile) (**4c**): Color: White. Yield: 70%. M.p.: 180-182 °C. Anal. calcd. for $C_{34}H_{24}N_4O_4S_2$: C, 66.22; H, 3.92; N, 9.08. Found: C, 65.90; H, 3.66; N, 8.75%. FT-IR (KBr, ν, cm^{-1}): 3209 (NH), 2206 (CN), 1690 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.60 (s, 6H, $2CH_3$), 3.96 (s, 6H, $2OCH_3$), 5.59 (s, 2H, $2CH_{olefenic}$), 7.28-7.50 (m, 8H, CH_{arom}), 9.20 (br, 2H, 2NH).

6, 6′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile) (**4d**): Color: Brown. Yield: 66%. M.p.: 208-210 °C. Anal. calcd. for $C_{32}H_{18}N_6O_6S_2$: C, 59.44; H, 2.81; N, 13.00. Found: C, 59.05; H, 2.66; N, 12.70%. FT-IR (KBr, ν, cm^{-1}): 3222 (NH), 2212 (CN), 1687 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.62 (s, 6H, $2CH_3$), 5.56 (s, 2H, $2CH_{olefenic}$), 7.38-7.56 (m, 8H, CH_{arom}), 9.24 (br, 2H, 2NH).

2.5. Synthesis of 1,1′-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(3-arylprop-2-en-1-one) (5a-d)

A mixture of compound **1** (0.252 g, 0.001 mol), aromatic aldehyde (0.002 mol) in absolute ethanol (25 mL) and sodium ethoxide (0.2 g, 0.003 mol) was refluxed for 1 h. Solvent was removed under vacuum and the solid mass was recrystallized from methanol into chalcone derivatives **5a**-**d** (Scheme 4).

1, 1′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-phenylprop-2-en-1-one) (**5a**): Color: White. Yield: 85%. M.p.: 208-210 °C. Anal. calcd. for $C_{26}H_{20}O_2S_2$: C, 72.87; H, 4.70. Found: C, 72.57; H, 4.40%. FT-IR (KBr, ν, cm^{-1}): 1696 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.25 (s, 6H, $2CH_3$), 7.32-7.56 (m, 10H, CH_{arom}), 8.18 (d, 2H, *J* = 12.8 Hz, $2CH_{ethylenic}$), 8.68 (d, 2H, *J* = 12.6 Hz, $2CH_{ethylenic}$). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.5, 113.5, 129.6, 129.9, 132.32, 133.2, 138.8, 141.5, 145.3, 147.5, 148.6, 186.5. MS (EI, *m/z* (%)): 428 (M^+, 80), 427 (M^+-1, 72), 413 (21), 274 (100).

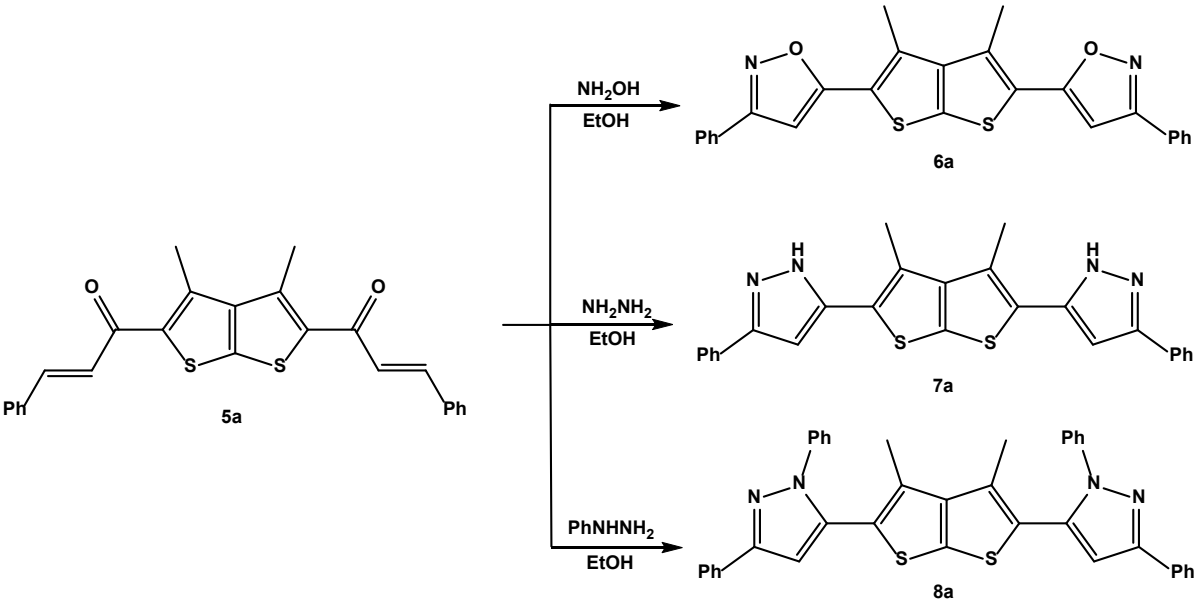
1, 1′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-(4-chlorophenyl)prop-2-en-1-one) (**5b**): Color: Yellow. Yield: 87%. M.p.: 262-264 °C. Anal. calcd. for $C_{26}H_{18}Cl_2O_2S_2$: C, 62.78; H, 3.65. Found: C, 62.45; H, 3.38%. FT-IR (KBr, ν, cm^{-1}): 1720 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 6H, $2CH_3$), 7.35-7.56 (m, 8H, CH_{arom}), 7.72 (d, 2H, *J* = 12.42, $2CH_{ethylenic}$), 8.66 (d, 2H, *J* = 12.6, $2CH_{ethylenic}$). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 14.9, 112.5, 125.5, 129.2, 131.2, 133.05, 134.6, 137.2, 142.2, 145.5, 148.7, 185.5. MS (EI, *m/z* (%)): 498 (M^+, 12), 496 (M^+-2, 18), 426 (100).

1, 1′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (**5c**): Color: Pale yellow. Yield: 64%. M.p.: 238-240 °C. Anal. calcd. for $C_{28}H_{24}O_4S_2$: C, 68.83; H, 4.95. Found: C, 68.65; H, 4.78%. FT-IR (KBr, ν, cm^{-1}): 1720 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.29 (s, 6H, $2CH_3$), 3.89 (s, 6H, $2OCH_3$), 7.32-7.50 (m, 8H, CH_{arom}), 7.96 (d, 2H, *J* = 12.6 Hz, $2CH_{ethylenic}$), 8.65 (d, 2H, *J* = 12.8 Hz, $2CH_{ethylenic}$).

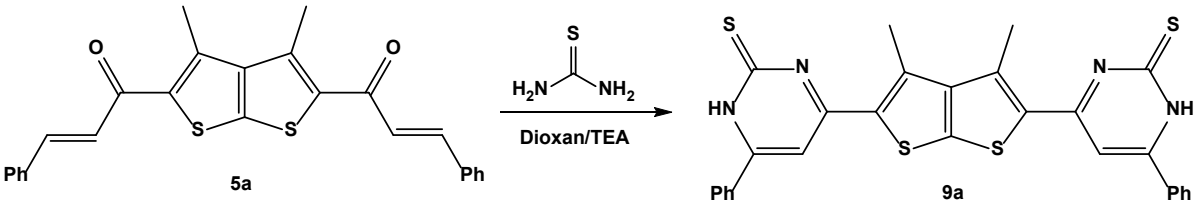
1, 1′-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-(4-nitrophenyl)prop-2-en-1-one) (**5d**): Color: Brown. Yield: 78%. M.p.: 268-270 °C. Anal. calcd. for $C_{26}H_{18}N_2O_6S_2$: C, 60.22; H, 3.50; N, 5.40. Found: C, 59.88; H, 3.22; N, 5.15%. FT-IR (KBr, ν, cm^{-1}): 1695 (CO). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 6H, $2CH_3$), 7.55-7.75 (m, 8H, CH_{arom}), 8.12 (d, 2H, *J* = 12.8 Hz, $2CH_{ethylenic}$), 8.80 (d, 2H, *J* = 12.6, $2CH_{ethylenic}$).

2.6. Synthesis of compounds 6a, 7a and 8a

A mixture of compound **5a** (0.43 g, 0.001 mol) and hydroxylamine, hydrazine and/or phenylhydrazine (0.0025 mol) was dissolved in ethanol (25 mL).



Scheme 5. Synthesis of *bis*-heterocycles **6a**-**8a**.



Scheme 6. Synthesis of 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)*bis*(6-phenylpyrimidine-2(1*H*)-thione), **9a**.

The reaction mixture was heated under reflux for 3 h. Solvent was removed under vacuum and water was added to the residual slurry and then left 2h. The formed solid was collected by filtration and recrystallized from ethanol to give compounds **6a**, **7a** and **8a**, respectively (Scheme 5).

5, 5'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-phenylisoxazole) (**6a**): Color: Yellow. Yield: 58%. M.p.: 108-110 °C. Anal. calcd. for $C_{26}H_{18}N_2O_2S_2$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.40; H, 3.66; N, 6.02%. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 6H, $2CH_3$), 6.68 (s, 2H, 2=CH), 7.26-7.50 (m, 10H, CH_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.2, 118.2, 122.5, 128.4, 132.1, 133.7, 138.2, 142.4, 147.1, 148.3, 153.1, 159.2.

5, 5'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(3-phenyl-1H-pyrazole) (**7a**): Color: White. Yield: 77%. M.p.: 143-145 °C. Anal. calcd. for $C_{26}H_{20}N_4S_2$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.70; H, 4.15; N, 12.12%. FT-IR (KBr, ν, cm^{-1}): 3195 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 4.85 (s, 2H, 2=CH), 7.25-7.55 (m, 10H, CH_{arom}), 10.12 (br, 2H, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.5, 112.5, 121.5, 127.5, 132.6, 133.4, 138.7, 142.3, 147.2, 148.5, 153.5, 156.8.

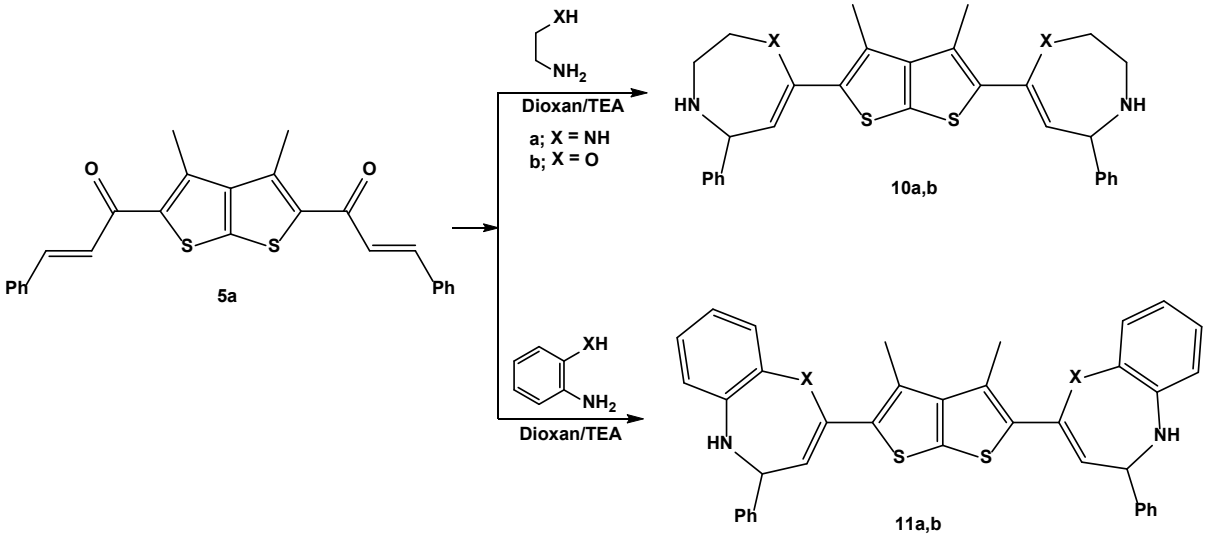
5, 5'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(1,3-diphenyl-1H-pyrazole) (**8a**): Color: Pale yellow. Yield: 75%. M.p.: 212-214 °C. Anal. calcd. for $C_{38}H_{28}N_4S_2$: C, 75.47; H, 4.67; N, 9.26. Found: C, 75.10; H, 4.38; N, 9.01%. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 4.80 (s, 2H, 2=CH), 7.28-7.55 (m, 20H, CH_{arom}).

2.7. Synthesis of 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(6-phenylpyrimidine-2(1H)-thione) (9a)

A mixture of compound **5a** (0.43 g, 0.001 mol) and thiourea (0.19 g, 0.0025 mol) in dioxane (25 mL) was treated with a catalytic amount of triethylamine. The reaction mixture was heated under reflux for 4 h, after the completion of the reaction (as monitored by TLC), solvent was removed under reduced pressure and the residual slurry was then triturated with light petroleum (40-60 °C) and the formed solid was collected and recrystallized from acetonitrile (Scheme 6). Color: Pale yellow. Yield: 65%. M.p.: 178-180 °C. Anal. calcd. for $C_{28}H_{20}N_4S_2$: 62.19; H, 3.73; N, 10.36. Found: C, 61.88; H, 3.50; N, 10.20%. FT-IR (KBr, ν, cm^{-1}): 3211 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 5.35 (s, 2H, 2=CH), 7.33-7.58 (m, 10H, CH_{arom}), 10.15 (br, 2H, 2NH).

2.8. Synthesis of compounds 10a, 10b, 11a and 11b

A mixture of compound **5a** (0.43 g, 0.001 mol) and ethylenediamine, ethanolamine, *o*-phenylenediamine and/or *o*-aminophenol (0.002 mol) in dioxane (25 mL) was treated with few drops of triethylamine as catalyst. The reaction mixture was then heated under reflux for 4 h. Solvent was evaporated under vacuum, the solid mass was then triturated with light petroleum ether (40-60 °C) and the formed solid was collected, recrystallized from acetonitrile into compounds **10a**,**b** and **11a**,**b**, respectively (Scheme 7).



Scheme 7. Synthesis of *bis*-heterocycles **10a**,**b** and **11a**,**b**.

7, 7'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(5-phenyl-2, 3, 4, 5-tetrahydro-1H-1, 4-diazepine) (**10a**): Color: Yellow. Yield: 75%. M.p.: 188-190 °C. Anal. calcd. for $C_{30}H_{32}N_4S_2$: C, 70.28; H, 6.29; N, 10.93. Found: C, 69.95; H, 5.90; N, 10.61%. FT-IR (KBr, ν, cm^{-1}): 3285, 3195 (2NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 3.63 (br, 4H, $2CH_2$), 3.93 (br, 4H, $2CH_2$), 4.85 (d, *J* = 4.8 Hz, 2H, CH), 5.65 (d, *J* = 5.6 Hz, 2H, =CH), 7.25-7.55 (m, 10H, CH_{arom}), 8.56 (br, 2H, 2NH), 10.12 (br, 2H, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.1, 53.8, 56.7, 66.5, 112.5, 118.6, 121.0, 123.1, 127.4, 128.5, 132.3, 138.1, 147.2, 148.4.

7, 7'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(5-phenyl-2, 3, 4, 5-tetrahydro-1,4-oxazepine) (**10b**): Color: Pale yellow. Yield: 78%. M.p.: 118-120 °C. Anal. calcd. for $C_{30}H_{30}N_2O_2S_2$: C, 70.01; H, 5.88; N, 5.44. Found: C, 70.12; H, 5.56; N, 5.20%. FT-IR (KBr, ν, cm^{-1}): 3215 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 3.62 (br, 4H, $2CH_2$), 3.96 (br, 4H, $2CH_2$), 4.88 (d, *J* = 4.8 Hz, 2H, 2CH), 5.60 (d, *J* = 5.8 Hz, 2H, 2=CH), 7.28-7.55 (m, 10H, CH_{arom}), 8.33 (br, 2H, 2NH).

4,4'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(2-phenyl-2, 5-dihydro-1H-benzo[b][1, 4]diazepine) (**11a**): Color: Yellow. Yield: 78%. M.p.: 166-168 °C. Anal. calcd. for $C_{38}H_{32}N_4S_2$: C, 74.97; H, 5.30; N, 9.20. Found: C, 74.56; H, 5.01; N, 8.87%. FT-IR (KBr, ν, cm^{-1}): 3265, 3189 (2NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.58 (s, 6H, $2CH_3$), 4.75 (d, *J* = 4.8 Hz, 2H, 2CH), 5.605 (d, *J* = 5.8 Hz, 2H, 2 =CH), 7.22-7.68 (m, 18H, CH_{arom}), 8.45 (br, 2H, 2NH), 10.15 (br, 2H, 2NH).

2, 2'-(3, 4-Dimethylthieno[2, 3-b]thiophene-2, 5-diyl)bis(4-phenyl-4, 5-dihydrobenzo[b][1, 4]oxazepine) (**11b**): Color: Pale yellow. Yield: 78%. M.p.: 186-188 °C. Anal. calcd. for $C_{38}H_{30}N_2O_2S_2$: C, 74.73; H, 4.95; N, 4.59. Found: C, 74.25; H, 4.66; N, 4.30%. FT-IR (KBr, ν, cm^{-1}): 3218 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (s, 6H, $2CH_3$), 4.85 (d, *J* = 4.6 Hz, 2H, 2CH), 5.66 (d, *J* = 5.6 Hz, 2H, 2=CH), 7.20-7.75 (m, 18H, CH_{arom}), 8.53 (br, 2H, 2NH).

2.9. Biological evaluation

The antibacterial activity of different compounds **2**, **3a-d**, **4a-d**, **6a**, **7a**, **9a**, **10a**,**b** and **11a**,**b** was determined by agar well diffusion method as described by Pandey [52]. Petri plates containing 20 mL of sterilized nutrient agar (NA) medium were seeded with 50 µL of 24 hr culture of the pathogenic bacterial strains (*Bacillus cereus*, *Bacillus subtilis, Klebsiella pneumonia, Escherichia coli, Serratia sp.* and *Pseudomonas aerugenosa*) and allowed to solidify. Sterile cork borer (6 mm diameter) was used to bore wells in the plates, compounds solutions (100 ppm) were carefully dispensed into the bored holes as well as solvent control. The plates were then incubated at 37 °C for 48 hours. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well (NCCLS) [53-55].

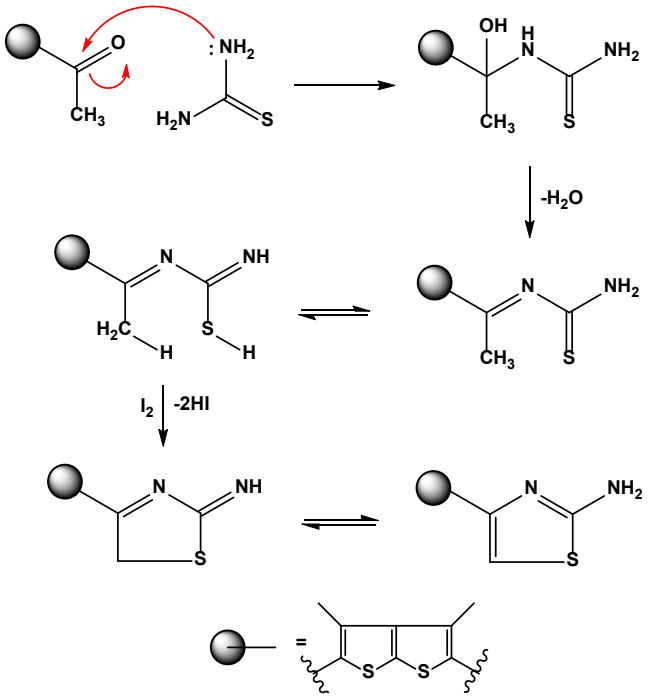
3. Results and discussion

3.1. Synthesis

In continuation of our work on the synthesis of thienothiophene derivatives [56-58], the starting compound 1,1'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)diethanone (**1**) was obtained *via* the one-pot reaction of acetylacetone, carbon disulfide and two equivalents of chloroacetone under phase transfer catalysis conditions [benzene/K_2CO_3/TBAB], Scheme 1. The structure of compound **1** was established on the basis of its elemental analyses and spectral data. Its IR spectrum revealed absorption bands at 1669 cm^{-1} due to carbonyl functions. The ^{1}H NMR spectrum displayed a singlet at δ 2.55 ppm, characteristic of acetyl protons as well as another singlet at δ 2.81 ppm characteristic for methyl protons, whereas its ^{13}C NMR δ 19.3 ($2CH_3$), 38.50 ($2CH_3$-acetyl), 131.7, 134.5, 143.4, 160.5 (thienothiophene), 191.2 ppm (2 C=O) and MS data 252 (M^+, 12%), 250 (100%), 164 (34%), 134 (18%).

The reaction of compound **1** with thiourea and iodine under solvent-free conditions afforded after working up 2, 2'-(3, 4-dimethylthieno[2, 3-b]thiophene-2, 5-diyl)dithiazol-5-amine (**2**) in good yield. Compound **2** was previously obtained [10] by treatment of *bis*-2-bromoacetylthieno[2,3-b]thiophene with thiourea in refluxing EtOH/TEA. The IR spectrum of compound **2** showed absorption maxima at 3398 and 3312 cm^{-1} characteristic for NH_2 group, where the ^{1}H NMR spectrum of compound **2** revealed a doublet of doublets at δ 6.80-7.13 ppm (2H, =CH thiazole), a singlet at δ 6.72 ppm for (4H, $2NH_2$) protons and a singlet at 2.59 ppm for (6H, CH_3 protons), Scheme 2.

The reaction mechanism of this reaction was assumed to proceed *via* a preliminary nucleophilic attack of the primary amine group of thiourea into the acetyl carbonyl group followed by oxidation using iodine to give the thiazole derivative, Scheme 8.



Scheme 8. The suggested reaction mechanism of compound **2**.

The one-pot reaction of compound **1**, aromatic aldehydes (two equivalents) and malononitrile (two equivalents) in ethanol in the presence of a catalytic amount of triethylamine as a catalyst afforded 6,6'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)bis(2-amino-4-aryl-*4H*-pyran-3-carbonitrile) (**3a-d**) in good yield. The reaction of compounds **3a-d** with ammonium acetate in acetic acid afforded the expected 6,6'-(3,4-dimethylthieno[2,3-b]thiophene-2, 5-diyl) *bis*(2-oxo-4-aryl-1,2-dihydropyridine-3-carbonitrile) derivatives (**4a-d**), Scheme 3. The IR spectrum of compound **3a** revealed characteristic bands at 3294, 3206 and 2212 cm^{-1} corresponding to NH_2 and CN groups respectively, whereas its ^1H NMR spectrum showed a broad band at δ 6.98-6.87 ppm for NH_2 proton. Where the IR spectrum of compound **4a** showed absorption bands at 3234, 2210 and 1688 cm^{-1} for NH, CN and C=O groups respectively, while its ^1H NMR spectrum revealed a broad band at δ 12.03 ppm for 2NH protons.

The reaction mechanism was proposed to proceed through a preliminary chalcone formation followed by a Michael addition of malononitrile and subsequent cyclisation, Scheme 9.

This aforementioned mechanism was supported by treatment of compound **1** with two equivalents of aromatic aldehyde in absolute ethanol in the presence of sodium ethoxide as a catalyst to give the corresponding chalcone derivatives **5a-d** then treatment of chalcone derivatives with malononitrile under alkaline conditions afforded the corresponding pyrane derivatives **3a-d**, Scheme 4.

Encouraged by the aforementioned results compound **5a** was allowed to react with different reagents *viz.* hydroxylamine, hydrazine and/or phenyl hydrazine, where the corresponding *bis*(five-membered ring heterocycles) namely: 5,5'-(3,4-dimethylthieno[2, 3-b]thiophene-2, 5-diyl)*bis*(3-phenylisoxazole) (**6a**), 5,5'-(3,4-dimethylthieno[2,3-b]thiophene-2, 5-diyl)bis(3-phenyl-1*H*-pyrazole) (**7a**) and 5, 5'-(3, 4-dimethylthieno[2, 3-b]thiophene-2, 5-diyl)*bis*(1, 3-diphenyl-*1H*-pyrazole) (**8a**) were obtained respectively, Scheme 5.

Treatment of compounds **5a** with thiourea in dioxane in the presence of a catalytic amount of triethylamine as catalyst resulted in the formation of the corresponding six-membered ring heterocycles namely 4,4'-(3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)*bis*(6-phenylpyrimidine-2(1*H*)-thione) (**9a**), Scheme 6.

Finally, compound **5a** was allowed to react with ethylene diamine, ethanolamine, *o*-phenylenediamine, and/or *o*-aminophenol in dioxane in the presence of triethylamine as catalyst to give the corresponding seven-membered ring heterocycles **10a**,**b** and **11a**,**b**, respectively, Scheme 7.

The reaction was thought to proceed *via* a preliminary nucleophilic attack of the amino group of the bifunctional reagent onto the chalcone ethylenic double bond followed by internal cyclisation by the other amino or hydroxyl group onto the carbonyl group followed by H_2O elimination.

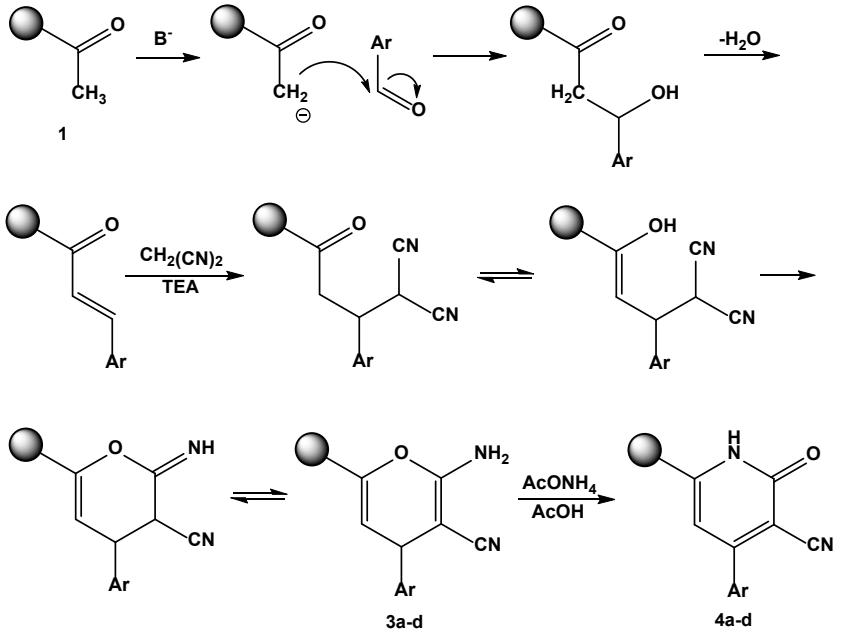
All synthesized compounds were obtained as pure solid crystals or powder with high yield. The structures of the obtained compounds were established by their elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectroscopy.

3.2. Biological evaluation

The antibacterial activity of compounds **2**, **3a-d**, **4a-d**, **6a**, **7a**, **9a**, **10a**,**b** and **11a**,**b** is represented by the diameters (mm) of inhibition zones (Table 1 and Figure 1). All compounds were found to be active against three among the six tested strains. Compounds **4b**, **4c**, **6a**, **9a** and **11b** was found to produce inhibition zones against *E. coli* and *Pseudomonas aerugenosa*; where compounds **7a**, **9a** and **10b** were active against *Pseudomonas aerugenosa* and *Klebsiella pneumonia*. Although it's known with its resistance to many antibiotics and antiseptics, remarkable activity towards *Pseudomonas aerugenosa* was recorded with the maximum inhibition zones (7 and 8 mm) for the synthesized compounds **2**, **3a-d**, **4a-d**, **6a**, **7a**, **9a**, **10a**,**b** and **11a**,**b**. *Pseudomonas aeruginosa* has a high degree of multidrug resistance related to the presence of antibiotic efflux systems providing resistance to multiple antimicrobial agents [54,55].

Table 1. The antibacterial activity of the newly synthesized compounds against some bacterial pathogens.

Compound	Antibacterial data in MIC (µg/mL)			Antifungal data in MIC (µg/mL)	
	E. coli	*P. aerugenosa*	*K. pneumonia*	*A. niger*	*A. fumigatus*
2	6	7	3	5	-
3a	4	5	7	-	-
3b	6	6	3	-	-
3c	5	5	4	-	-
3d	0	7	7	5	3
4a	8	7	5	-	-
4b	7	8	6	-	-
4c	8	6	8	-	-
4d	5	5	6	6	5
6a	5	7	0	-	-
7a	6	8	2	-	-
9a	0	8	6	-	-
10a	5	7	6	-	-
10b	0	8	7	-	-
11a	2	7	6	-	-
11b	5	8	6	-	-
Streptomycin	10	12	10	-	-
Fluconazole	-	-	-	20	22



Scheme 9. Suggested reaction pathway for the formation of compounds **4a**-**d**.

Figure 1. Antibacterial activity of compounds **6a**, **9a** and **10b** against different pathogenic bacterial strains.

4. Conclusion

We developed a direct and straightforward strategy for the synthesis of some new *bis*(chalcone) derivatives and studied the significance of this class of compounds as versatile synthons for new *bis*(thiazole), *bis*(pyran), *bis*(isoxazoles), *bis*(pyrazoles), *bis*(pyrimidines) and *bis*(diazepines, oxazepines, benzodiazepines and benzoxazepines). Due to the mild reaction conditions, good yields as well as easily accessible starting material, the synthetic approaches discussed here should provide access for new class of *bis*(functionalized) heterocycles. The new synthesized compounds were subjected for studying their pharmacological and biological activities. Compounds **4b**, **4c**, **7a**, **6a**, **9a** and **11b** were found to be very potent against *P. aeruginosa, E. coli and K. pneumonia*.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

ORCID

Mounir Abbas Ali Mohamed
http://orcid.org/0000-0001-7080-8505
Hanan Salah
http://orcid.org/0000-0003-3645-0874
Ahmed Mohamed Mohamed El-Saghier
http://orcid.org/0000-0002-4338-1486

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