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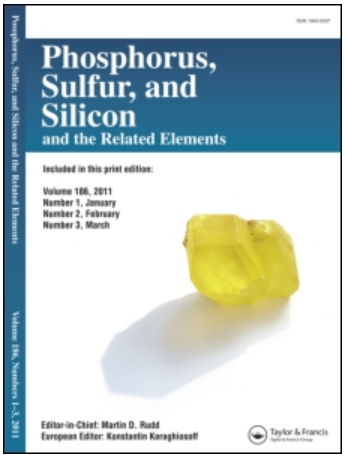

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Studies on 2-Aminothiophenes: Synthesis, Transformations, and Biological Evaluation of Functionally-Substituted Thiophenes and Their Fused Derivatives

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Studies on 2-Aminothiophenes: Synthesis, Transformations, and Biological Evaluation of Functionally-Substituted Thiophenes and Their Fused Derivatives

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*Heterocyclic enamines **1** reacted with ethyl acetoacetate to afford the corresponding amide derivatives **2**. Treatment of **2** with carbon disulphide yielded the dipotassium salts **3** which reacted in-situ with a variety of α-haloketones to give the respective substituted thiophenes **5**, **8**, and **13**. The reactivity of the latter products towards various chemical reagents was studied to yield their fused thiophene derivatives **7**, **10**, **12**, and **14**, respectively. Some representative compounds were tested for antimicrobial activity.*

Keywords 2-Aminothiophenes; α-haloketons; antimicrobial activities; enamines; fused thiophenes

INTRODUCTION

Substituted thiophenes have been of recent interest due to their diverse biological effects. Several of them have been found to display

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antibacterial,[1–3] antifungal,[4] anti-amoebic,[5] antioxidant,[6] antitumor,[7] anticoagulant and antithrombotic[8] activities. Others have been used as anti-inflammatory,[9] antituberculosis,[10,11] analgesic,[12] antirheumatic[13] antiprotozoal,[14] and antimalarial[15] agents. In addition, such a ring system has demonstrated to be effective for the treatment of migraine,[16] depression,[17] chronic hepatitis C virus (HCV),[18] and Alzheimer's disease (AD)[19] as well. On the other hand, fused thiophenes have been also reported to be biologically versatile compounds having antimicrobial,[20,21] antitumor,[22] antiviral,[23] and anti-inflammatory[24] characteristics, and moreover found to be useful as bactericidals[25,26] and antiprotozoals,[27] as well as intercalating nucleic acids (INA).[28] Therefore, the fusion of some heterocyclic moieties to the thiophene ring leads to new heterocycles which might show enhanced biological activities. In light of all these considerations, and in continuation of our long-term interest in the chemistry of the benzo[*b*]thiophenes,[29–31] we wish to report herein on the scope and applicability of the 2-amino-5,5-dimethyl-7-oxotetrahydrobenzo[*b*]thiophenes **1a**, **b** for their heterocyclization with some α-haloketones. The work has resulted in the formation of several new functionally-substituted thiophenes which could also be annulated into fused heterocyclic ring systems with anticipated bio-activities.

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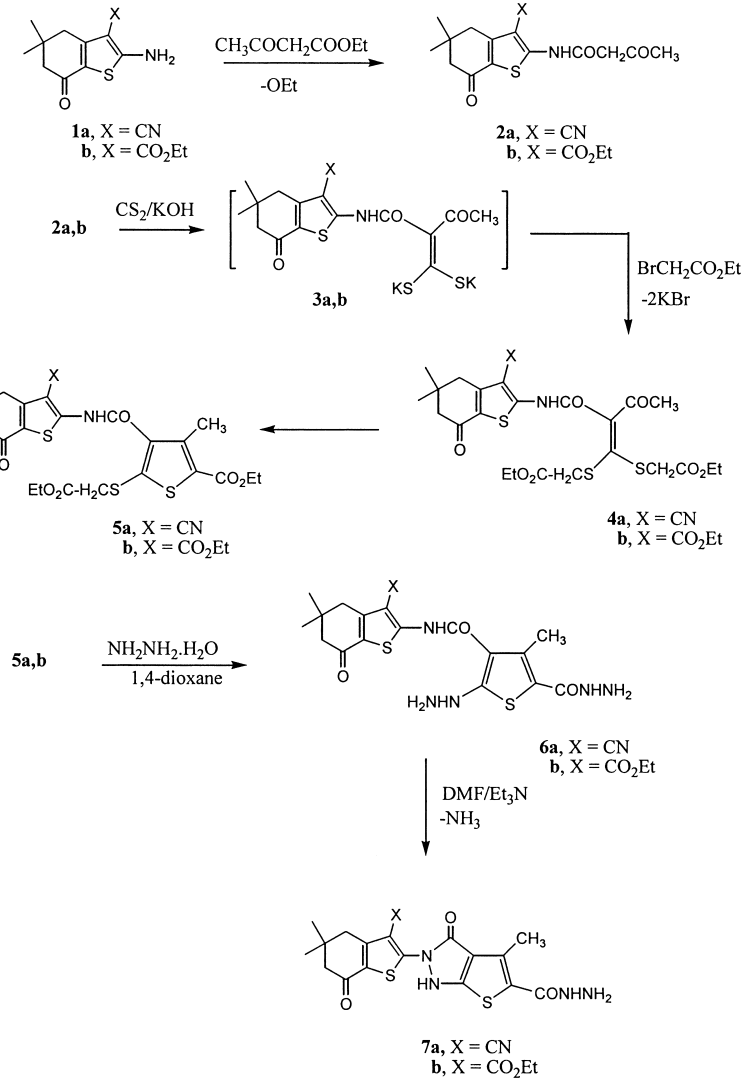
RESULTS AND DISCUSSION

Heterocyclic β-enaminonitrile derivative **1a** and its β-ester analogue **1b**[32,33] reacted with ethyl acetoacetate to give the acyclic amide derivatives **2a**, **b**, respectively. The structure of the latter products was based on analytical and spectral data. Thus, the ^{13}C NMR spectrum of **2a** showed δ 26.7, 26.9 ($2CH_3$), 32.1 (CH_3), 54.8, 67.3, 82.9 ($3CH_2$), 88.0 (cyclohexanone-C_5), 119.9 (CN), 122.4, 124.8, 140.1, 143.7 (thiophene-C), 177.2, 179.5, 180.2 (3CO). It has been found that the base-promoted nucleophilic addition of **2a**, **b** to equimolar amounts of carbon disulphide, in dimethylformamide solutions containing potassium hydroxide, gave the respective non-isolable dipotassium disulphide salts **3a**, **b** (Scheme 1).

The versatility of these intermediate salts **3** was proved by studying their reactivity towards various α-halo compounds, namely, ethyl bromoacetate, chloroacetone, and bromoacetonitrile, respectively, with respect to the synthesis of highly substituted thiophenes. Thus, in-situ heterocyclization of the non-isolable salts **3a**, **b** with ethyl bromoacetate gave the corresponding thiophene derivatives **5a**, **b**, respectively. The reaction apparently involves formation of the intermediates **4a**, **b**. Our trials to isolate the latter intermediates were unsuccessful if



SCHEME 1

the reaction was kept overnight in its medium. However, under TLC controlled reaction, the acyclic intermediates **4a**, **b** were isolated and characterized (see experimental section). Compounds **4a**, **b** seemed to be unstable as they underwent ready cyclisation to **5a**, **b** upon warming in ethanol solution. The structure of the thiophene derivatives **5a**, **b** was based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of

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5a showed, besides the expected signals for the cyclohexanone moiety, a singlet at δ 2.77 for CH_3 group, two triplets at δ 1.13, 1.16 for two ester CH_3 groups, two quartets at δ 4.19, 4.23 for two ester CH_2 groups, and a singlet at δ 4.99 for CH_2 group. Interestingly, the thiophene products **5** seemed to be useful precursors for further chemical transformations. Thus, treatment of **5a**, **b** with hydrazine hydrate gave the corresponding 5-hydrazido-2-hydrazinothiophene derivatives **6a**, **b**, whose structures were based on the analytical and spectral data. Thus, the ^{1}H NMR spectrum of **6a** showed, besides the regular signals, D_2O-exchangeable signals at δ 5.21, 7.92, 8.32 for two NH_2 groups and three NH groups, respectively. The hydrazino derivatives **6a**, **b** proved to be interesting candidates for the synthesis of fused pyrazoles. Thus, they could be cyclized, when heated in dimethylformamide solutions containing triethylamine, into the respective thieno[2,3-*c*]pyrazole derivatives **7a**, **b**, respectively, via loss of an ammonia molecule, in each case (Scheme 1). The structure of the latter products was based on analytical and spectral data. Thus, the ^{13}C NMR spectrum of **7a** showed the presence of δ 26.5, 26.6 ($2CH_3$), 32.4 (CH_3), 54.4, 67.0 ($2CH_2$), 88.5 (cyclohexanone-C_5), 120.3 (CN), 122.2, 122.9, 123.6, 125.4, 140.0, 143.6, 144.1, 144.2 (two thiophene-C), 177.7, 179.4, 180.0 (3CO).

As an extension of such synthetic route, the behavior of the non-isolable dipotassium disulphide salts **3** towards another α-haloketone was examined. Thus, subsequent treatment of **3a**, **b** with chloroacetone provided the corresponding 5-acetyl-4-methyl-2-oxopropylsulfanylthiophene derivatives **8a**, **b**, respectively (Scheme 2). Their structures were based on the analytical and spectral data (c.f. Experimental section). The structure of the products **8** have been further established by studying their reactivity towards different nucleophilic reagents. Thus, reactions of the precursor aceto derivatives **8a**, **b** with malononitrile gave the thiophene derivatives **9a**, **b**, respectively. The mechanism for the formation of **9** may be seen, in each case, as a sequence of condensation of the active methylene group in malononitrile with the carbonyl acetyl group in **8** and subsequent nucleophilic displacement of the labile thioether moiety in **8** by another molecule of malononitrile. Refluxing of compounds **9a**, **b** in sodium ethoxide solutions resulted in their heterocyclization into the corresponding thieno[3,2-*c*]pyridine derivatives **10a**, **b**, respectively. Furthermore, the aceto derivatives **8** proved to be also highly reactive towards a different nucleophile. Thus, when compounds **8a**, **b** were allowed to react with hydrazine hydrate, it furnished the corresponding 2-hydrazino-5-hydrazonoethylthiophene derivatives **11a**, **b**, respectively.

The reactivity of the hydrazino derivatives **11** towards formation of fused pyrazoles was investigated via their heterocyclization, in

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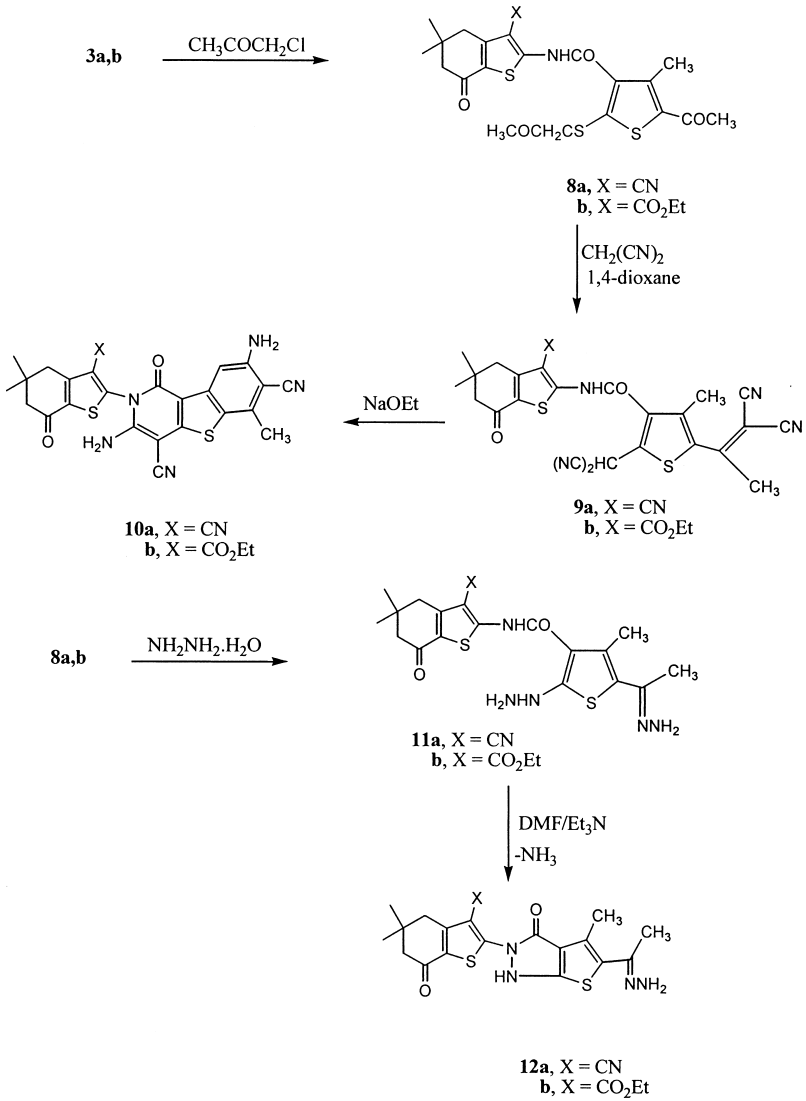

SCHEME 2

dimethylformamide solutions containing triethylamine, to give the respective thieno[2,3-*c*]pyrazole derivatives **12a**, **b**, respectively (Scheme 2). Structures of compounds **11a**, **b** and **12a**, **b** were based on analytical and spectral data (c.f. Experimental section). It seemed that reactions of the aceto derivatives **8** with various nucleophiles constitute easy and

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convenient routes leading to fused pyridines and fused pyrazoles, which are otherwise difficult to access.

Finally, the applicability and generality of the intermediate salts **3** for the formation of thiophenes was further explored. Similarly, it has been found that they readily underwent in-situ heterocyclization upon treatment with bromoacetonitrile to produce the thiophene derivatives **13a**, **b** (Scheme 3). The ^{13}C NMR spectrum of **13a** showed the presence of δ 26.2, 26.5, 30.1 ($3CH_3$), 44.8, 54.2, 67.7 ($3CH_2$), 88.5 (cyclohexanone-C_5), 120.2, 120.4, 120.7 (3CN), 121.8, 122.4, 124.7, 142.0, 142.8, 143.6, 143.8, 144.6 (two thiophene-C), 179.8, 180.3 (2CO). It has been reported[34–36] that a methyl group, situated in the ortho-position to an electron withdrawing heteroatomic nitrile, shows an interesting reactivity towards electrophilic reagents. Thus, compounds **13a**, **b** reacted with elemental sulfur to afford the thieno[3,4-*b*]thiophene derivatives **14a**, **b**, respectively (Scheme 3). The structure of the latter products was based on analytical and spectral data (c.f. Experimental section).

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EXPERIMENTAL

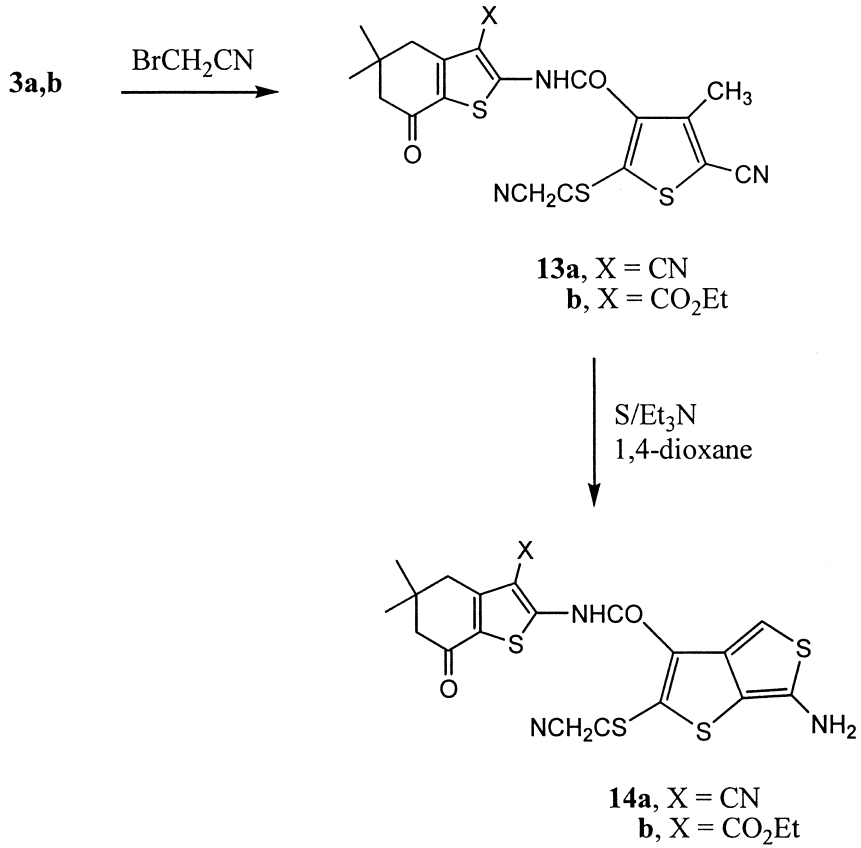
Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. Mass spectra were recorded using AEI MS 30 mass spectrometer operating at 70 eV. Compounds **1a,**, **b** were prepared according to the literature procedures.[32,33]

General Procedure for the Synthesis of (2a,b)

Equimolar amounts (0.01 mol) of enamine **1a** or **1b**, and ethyl acetoacetate, in 1,4-dioxane (60 ml) containing a catalytic amount of triethylamine (1.0 ml), was heated under reflux, for 4 h then left to cool at room temperature. A dilute solution of hydrochloric acid was added to bring the reaction mixture to pH 7. The precipitated product, in each case, was collected by filtration, dried in the air and crystallized from the proper solvent.

2-(Acetoacetamido)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (2a)

Orange crystals (from AcOH), yield 79% (2.40 g), m.p. 180-182°C. IR (ν/cm^{-1}) = 3460–3320 (NH), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696–1683 (3CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.14 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 8.83 (s, 1H,



SCHEME 3

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NH, D_2O-exchangeable). ^{13}C NMR δ = 26.7, 26.9 ($2CH_3$), 32.1 (CH_3), 54.8, 67.3, 82.9 ($3CH_2$), 88.0 (cyclohexanone-C_5), 119.9 (CN), 122.4, 124.8, 140.1, 143.7 (thiophene-C), 177.2, 179.5, 180.2 (3CO). MS: *m/z* (%) = 304 (M^+, 26%). $C_{15}H_{16}N_2O_3S$ (304.37): Calcd: C, 59.19; H, 5.30; N, 9.20; S, 10.54; Found: C, 58.99; H, 5.32; N, 9.15; S, 10.43.

Ethyl 2-(Acetoacetamido)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (2b)

Reddish brown crystals (form AcOH), yield 66% (2.32 g), m.p. 223–225°C. IR (ν/cm^{-1}) = 3490–3330 (NH), 2973–2890 (CH_3, CH_2), 1705–1680 (4CO), 1630 (C=C). ^1H NMR δ = 1.13 (t, J = 6.88 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.21 (s, 3H, CH_3), 4.22 (q, J = 6.88 Hz, 2H, CH_2), 4.53 (s, 2H, CH_2),

8.86 (s, 1H, NH, D_2O-exchangeable). $C_{17}H_{21}NO_5S$ (351.42): Calcd: C, 58.10; H, 6.02; N, 3.99; S, 9.12; Found: C, 58.01; H, 5.92; N, 4.01; S, 9.06.

Gerneral Procedure for the Synthesis of (4a,b)

To a solution of either **2a** or **2b** (0.01 mol), in DMF (30 ml) containing KOH (0.56 g, 0.01 mol), carbon disulphide (0.76 g, 0.01 mol) was added. The reaction mixture was stirred at room temperature overnight and then ethyl bromoacetate (0.01 mol) was added with continuous stirring at room temperature. After 2 h the reaction was stopped through its pouring onto ice/water containing HCl to bring the reaction mixture to pH 7. The precipitated product, in each case, was filtered off and washed with diethyl ether.

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2-[(4,4-Diethoxycarbonylmethylsulfanyl-2-oxo-3-buten-3-yl)-3-carbonylamino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (4a)

Yellow crystals (washed with diethyl ether), yield 60% (3.13 g), m.p. 78°C. IR (ν/cm^{-1}) = 3453–3317 (NH), 2974–2880 (CH_3, CH_2), 2222 (CN), 1703–1680 (5CO), 1639 (C=C). ^{1}H NMR δ = 1.14, 1.16 (2t, J = 6.36, 6.99 Hz, 6H, $2CH_3$), 1.66, 1.73 (2s, 6H, $2CH_3$), 2.69, 2.96 (2m, 4H, $2CH_2$), 2.77 (s, 3H, CH_3), 4.22, 4.25 (2q, J = 6.36, 6.99 Hz, 4H, $2CH_2$), 4.45, 4.99 (2s, 4H, $2CH_2$), 8.80 (s, 1H, NH, D_2O-exchangeable). $C_{24}H_{28}N_2O_7S_3$ (552.69): Calcd: C, 52.16; H, 5.11; N, 5.04; S, 17.41; Found: C, 52.43; H, 4.73; N, 5.22; S, 17.81.

Ethyl 2-[(4,4-Diethoxycarbonylmethylsulfanyl-2-oxo-3-buten-3-yl)-3-carbonylamino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4b)

Yellow crystals (washed with diethyl ether), yield 55% (3.29 g), m.p. 55–57°C. IR (ν/cm^{-1}) = 3463–3319 (NH), 2977–2883 (CH_3, CH_2), 1703–1676 (6CO), 1641 (C=C). ^{1}H NMR δ = 1.13, 1.14, 1.16 (3t, J = 6.46, 6.41, 7.04 Hz, 9H, $3CH_3$), 1.68, 1.72 (2s, 6H, $2CH_3$), 2.67, 2.95 (2m, 4H, $2CH_2$), 2.78 (s, 3H, CH_3), 4.20, 4.24, 4.28 (3q, J = 6.46, 6.41, 7.04 Hz, 6H, $3CH_2$), 4.42, 4.97 (2s, 4H, $2CH_2$), 8.82 (s, 1H, NH, D_2O-exchangeable). $C_{26}H_{33}NO_9S_3$ (599.74): Calcd: C, 52.07; H, 5.55; N, 2.34; S, 16.04; Found: C, 52.48; H, 5.22; N, 2.21; S, 15.87.

General Procedure for the Synthesis of (5a,b; 8a,b; and 13a,b)

To a solution of either **2a** or **2b** (0.01 mol), in DMF (30 ml) containing KOH (0.56 g, 0.01 mol), carbon disulphide (0.76 g, 0.01 mol) was added.

The reaction mixture was stirred at room temperature overnight and then the appropriate α-halo compound (0.02 mol) was added. The whole reaction mixture was stirred at room temperature for further 24 h, then poured onto iced water containing a few drops of dilute HCl to bring the reaction mixture to pH 7. The precipitated product, in each case, was filtered off and crystallized from the proper solvent.

2-[(5-Ethoxycarbonyl-2-ethoxycarbonylmethylsulfanyl-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (5a)

Yellow crystals (from EtOH), yield 74% (3.96 g), m.p. 188°C. IR (ν/cm^{-1}) = 3460–3320 (NH), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696–1683 (4CO), 1640 (C=C). ^{1}H NMR δ = 1.13, 1.16 (2t, J = 6.48, 7.01 Hz, 6H, $2CH_3$), 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 2.77 (s, 3H, CH_3), 4.19, 4.23 (2q, J = 6.48, 7.01Hz, 4H, $2CH_2$), 4.99 (s, 2H, CH_2), 8.79 (s, 1H, NH, D_2O-exchangeable). $C_{24}H_{26}N_2O_6S_3$ (534.67): Calcd: C, 53.91; H, 4.90; N, 5.24; S, 17.99; Found: C, 54.03; H, 4.80; N, 5.35; S, 17.71.

Ethyl 2-[(5-Ethoxycarbonyl-2-ethoxycarbonylmethylsulfanyl-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (5b)

Yellow crystals (from EtOH), yield 70% (4.07 g), m.p. 154°C. IR (ν/cm^{-1}) = 3490–3330 (NH), 2973–2890 (CH_3, CH_2), 1705–1680 (5CO), 1630 (C=C). ^{1}H NMR δ = 1.13, 1.15, 1.18 (3t, J = 6.05, 6.88, 7.03Hz, 9H, $3CH_3$), 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 2.77 (s, 3H, CH_3), 4.19, 4.21, 4.23 (3q, J = 6.05, 6.88, 7.03Hz, 6H, $3CH_2$), 4.99 (s, 2H, CH_2), 8.81 (s, 1H, NH, D_2O-exchangeable). $C_{26}H_{31}NO_8S_3$ (581.72): Calcd: C, 53.68; H, 5.37; N, 2.41; S, 16.54; Found: C, 53.49; H, 5.25; N, 2.35; S, 16.27.

2-[5-Acetyl-4-methyl-2-(2-oxopropylsulfanyl)thiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (8a)

Orange crystals (from AcOH), yield 66% (3.13 g), m.p. 104°C. IR (ν/cm^{-1}) = 3460–3320 (NH), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696–1683 (4CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 2.87, 3.23, 3.29 (3s, 9H, $3CH_3$), 5.34 (s, 2H, CH_2), 8.41 (s, br, 1H, NH, D_2O-exchangeable). $C_{22}H_{22}N_2O_4S_3$ (474.62): Calcd: C, 55.67; H, 4.67; N, 5.90; S, 20.27; Found: C, 55.50; H, 4.52; N, 5.74; S, 20.01.

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Ethyl 2-[5-Acetyl-4-methyl-2-(2-oxopropylsulfanyl)thiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (8b)

Orange crystals (from AcOH), yield 69% (3.60 g), m.p. 178°C. IR (ν/cm^{-1}) = 3490–3330 (NH), 2973–2890 (CH_3, CH_2), 1705–1680 (5CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.66 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, 2CH_3), 2.70, 2.88 (2m, 4H, 2CH_2), 2.87, 3.23, 3.29 (3s, 9H, 3CH_3), 4.22 (q, J = 6.66 Hz, 2H, CH_2), 5.34 (s, 2H, CH_2), 8.44 (s, br, 1H, NH, D_2O-exchangeable). $C_{24}H_{27}NO_6S_3$ (521.67): Calcd: C, 55.26; H, 5.22; N, 2.68; S, 18.44; Found: C, 55.30; H, 5.52; N, 2.44; S, 18.21.

2-[(5-Cyano-2-cyanomethylsulfanyl-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (13a)

Orange crystals (from EtOH), yield 75% (3.30 g), m.p. 122°C. IR (ν/cm^{-1}) = 3460–3320 (NH), 2960–2875 (CH_3, CH_2), 2222–2218 (3CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, 2CH_3), 2.68, 2.99 (2m, 4H, 2CH_2), 3.12 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 8.82 (s, br, 1H, NH, D_2O-exchangeable). ^{13}C NMR δ = 26.2, 26.5, 30.1 (3CH_3), 44.8, 54.2, 67.7 (3CH_2), 88.5 (cyclohexanone-C_5), 120.2, 120.4, 120.7 (3CN), 121.8, 122.4, 124.7, 142.0, 142.8, 143.6, 143.8, 144.6 (two thiophene-C), 179.8, 180.3 (2CO). MS: m/z (%) = 440 (M^+, 18%). $C_{20}H_{16}N_4O_2S_3$ (440.56): Calcd: C, 54.52; H, 3.66; N, 12.72; S, 21.84; Found: C, 54.25; H, 3.78; N, 12.97; S, 21.80.

Ethyl 2-[(5-Cyano-2-cyanomethylsulfanyl-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (13b)

Yellow crystals (from EtOH), yield 77% (3.75 g), m.p. 80°C. IR (ν/cm^{-1}) = 3490–3330 (NH), 2973–2890 (CH_3, CH_2), 2222, 2220 (2CN), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.41 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, 2CH_3), 2.70, 2.88 (2m, 4H, 2CH_2), 3.12 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.22 (q, J = 6.41 Hz, 2H, CH_2), 8.80 (s, br, 1H, NH, D_2O-exchangeable). $C_{22}H_{21}N_3O_4S_3$ (487.62): Calcd: C, 54.19; H, 4.34; N, 8.62; S, 19.73; Found: C, 54.29; H, 4.30; N, 8.43; S, 19.65.

General Procedure for the Synthesis of (6a,b and 11a,b)

A mixture of either **5a**, **b** or **8a**, **b** (0.01 mol) and hydrazine hydrate (0.03 mol) in 1,4-dioxane (30 ml) was heated under reflux for 3 h. The reaction mixture was left to cool at room temperature, poured over ice-cold water and allowed to stand overnight at 0–5°C. The formed precipitates were filtered off, washed with water, and crystallized from the appropriate solvents.

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2-[(5-Hydrazido-2-hydrazino-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (6a)

Buff crystals (from 1,4-dioxane), yield 77% (3.33 g), m.p. 222–225°C. IR (ν/cm^{-1}) = 3460–3320 (3NH, $2NH_2$), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696–1683 (3CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.12 (s, 3H, CH_3), 4.59, 5.21, (2s, 4H, $2NH_2$, D_2O-exchangeable) 7.92, 8.32, 8.79 (3s, 3H, 3NH, D_2O-exchangeable). $C_{18}H_{20}N_6O_3S_2$ (432.52): Calcd: C, 49.98; H, 4.66; N, 19.43; S, 14.83; Found: C, 50.29; H, 4.62; N, 19.32; S, 14.78.

Ethyl 2-[(5-Hydrazido-2-hydrazino-4-methylthiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (6b)

Buff crystals (from 1,4-dioxane), yield 73% (3.50 g), m.p. 167°C. IR (ν/cm^{-1}) = 3490–3330 (3NH, $2NH_2$), 2973–2890 (CH_3, CH_2), 1705–1680 (4CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.90 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.12 (s, 3H, CH_3), 4.22 (q, J = 6.90 Hz, 2H, CH_2), 4.59, 5.21 (2s, 4H, $2NH_2$, D_2O-exchangeable), 6.88, 8.32, 8.79 (3s, 3H, 3NH, D_2O-exchangeable). $C_{20}H_{25}N_5O_5S_2$ (479.58): Calcd: C, 50.09; H, 5.25; N,14.60; S, 13.37; Found: C, 50.34; H, 5.31; N, 14.64; S, 13.21.

2-{[2-Hydrazino-5-(1-hydrazonoethyl)-4-methylthiophene-3-carbonyl]amino}-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (11a)

Brown crystals (from 1,4-dioxane), yield 85% (3.66 g), m.p. 177°C. IR (ν/cm^{-1}) = 3460–3320 (2NH, $2NH_2$), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.05, 3.12 (2s, 6H, $2CH_3$) 4.56, 5.32 (2s, 4H, $2NH_2$, D_2O-exchangeable), 8.82, 9.04 (2s, br, 2H, 2NH, D_2O-exchangeable). $C_{19}H_{22}N_6O_2S_2$ (430.55): Calcd: C, 53.00; H, 5.15; N, 19.52; S, 14.90; Found: C, 53.25; H, 5.27; N, 19.56; S, 15.00.

Ethyl 2-{[2-Hydrazino-5-(1-hydrazonoethyl)-4-methylthiophene-3-carbonyl]amino}-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (11b)

Yellow crystals (from 1,4-dioxane), yield 80% (3.82 g), m.p. 122°C. IR (ν/cm^{-1}) = 3490–3330 (2NH, $2NH_2$), 2973–2890 (CH_3, CH_2), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 7.01 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.05, 3.12 (2s, 6H, $2CH_3$), 4.22 (q, J = 7.01 Hz, 2H, CH_2), 4.60, 5.39 (2s, 4H, $2NH_2$,

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D_2O-exchangeable), 8.41, 8.89 (2s, br, 2H, 2NH, D_2O-exchangeable). $C_{21}H_{27}N_5O_4S_2$ (477.60): Calcd: C, 52.81; H, 5.70; N, 14.66; S, 13.43; Found: C, 52.64; H, 5.73; N, 14.90; S, 13.30.

General Procedure for the Synthesis of (7a,b and 12a,b)

A solution of either **6a**, **b** or **11a**, **b** (0.005 mol) in DMF (30 ml), containing a catalytic amount of triethylamine (3 drops) was heated, under reflux, for 6 h and then left to cool at room temperature. The reaction mixture was poured onto iced water, and neutralized with dilute HCl (pH 7). The resulting solid product, in each case, was filtered off and crystallized from the proper solvent.

2-(5-Hydrazido-4-methyl-3-oxo-1,3-dihydrothieno[2,3-c]-pyrazol-2-yl)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (7a)

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Yellowish brown crystals (from 1,4-dioxane), yield 55% (1.14 g), m.p. > 300°C. IR (ν/cm^{-1}) = 3460–3320 (2NH, NH_2), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696–1683 (3CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.12 (s, 3H, CH_3), 5.85 (s, 2H, NH_2, D_2O-exchangeable), 8.45, 8.98 (2s, 2H, 2NH, D_2O-exchangeable). ^{13}C NMR δ = 26.5, 26.6 ($2CH_3$), 32.4 (CH_3), 54.4, 67.0 ($2CH_2$), 88.5 (cyclohexanone-C_5), 120.3 (CN), 122.2, 122.9, 123.6, 125.4, 140.0, 143.6, 144.1, 144.2 (two thiophene-C), 177.7, 179.4, 180.0 (3CO). $C_{18}H_{17}N_5O_3S_2$ (415.49): Calcd: C, 52.03; H, 4.12; N, 16.86; S, 15.44; Found: C, 51.90; H, 4.18; N, 17.01; S, 15.42.

Ethyl 2-(5-Hydrazido-4-methyl-3-oxo-1,3-dihydrothieno[2,3-c]pyrazol-2-yl)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (7b)

Pale yellow crystals (from DMF), yield 49% (1.13 g), m.p. 108–111°C. IR (ν/cm^{-1}) = 3490–3330 (2NH, NH_2), 2973–2890 (CH_3, CH_2), 1705–1680 (4CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 7.02 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.12 (s, 3H, CH_3), 4.22 (q, J = 7.02 Hz, 2H, CH_2), 5.91 (s, 2H, NH_2, D_2O-exchangeable), 8.56, 9.01 (2s, 2H, 2NH, D_2O-exchangeable). $C_{20}H_{22}N_4O_5S_2$ (462.55): Calcd: C, 51.93; H, 4.79; N, 12.11; S, 13.87; Found: C, 51.89; H, 4.73; N, 11.94; S, 13.77.

2-[5-(1-Hydrazonoethyl)-4-methyl-3-oxo-1,3-dihydrothieno[2,3-c]pyrazol-2-yl]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (12a)

Yellowish brown crystals (from AcOH), yield 54% (1.12 g), m.p. 221–223°C. IR (ν/cm^{-1}) = 3460–3320 (NH, NH_2), 2960–2875 (CH_3, CH_2), 2222 (CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s,

6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.05, 3.12 (2s, 6H, $2CH_3$), 5.66 (s, 2H, NH_2, D_2O-exchangeable), 8.21 (s, 1H, NH, D_2O-exchangeable). $C_{19}H_{19}N_5O_2S_2$ (413.52): Calcd: C, 55.19; H, 4.63; N, 16.94; S, 15.51; Found: C, 55.46; H, 4.70; N, 17.02; S, 15.69.

Ethyl 2-[5-(1-Hydrazonoethyl)-4-methyl-3-oxo-1,3-dihydrothieno[2,3-c]pyrazol-2-yl]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (12b)

Pale yellow crystals (from AcOH), yield 64% (1.47 g), m.p. 201–203°C. IR (ν/cm^{-1}) = 3490–3330 (NH, NH_2), 2973–2890 (CH_3, CH_2), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.99 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.05, 3.12 (2s, 6H, $2CH_3$), 4.22 (q, J = 6.99 Hz, 2H, CH_2), 5.65 (s, 2H, NH_2, D_2O-exchangeable), 8.82 (s, 1H, NH, D_2O-exchangeable). $C_{21}H_{24}N_4O_4S_2$ (460.57): Calcd: C, 54.76; H, 5.25; N, 12.16; S, 13.92; Found: C, 54.89; H, 5.35; N, 12.04; S, 13.86.

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General Procedure for the Synthesis of (9a,b)

Equimolar amounts (0.01 mol) of either **8a** or **8b** and malononitrile in 1,4-dioxane (30 ml) containing a catalytic amount of Et_3N (3 drops) were heated, under reflux, for 3 h. The reaction mixture was concentrated under vacuo, whereby the obtained solid product, in each case, was filtered off and crystallized from the proper solvent.

2-{[2-Dicyanomethyl-5-(2,2-dicyano-1-methylvinyl)-4-methylthiophene-3-carbonyl]amino}-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (9a)

Yellowish brown crystals (from AcOH—H_2O), yield 77% (3.84 g), m.p. >300°C. IR (ν/cm^{-1}) = 3460–3320 (NH), 2960–2875 (CH_3, CH_2), 2227–2218 (5CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.12, 3.45 (2s, 6H, $2CH_3$), 6.56 (s, 1H, CH), 8.42 (s, br, 1H, NH, D_2O-exchangeable). $C_{25}H_{18}N_6O_2S_2$ (498.58): Calcd: C, 60.22; H, 3.64; N, 16.86; S, 12.86; Found: C, 60.02; H, 3.70; N, 17.01; S, 12.63.

Ethyl 2-{[2-Dicyanomethyl-5-(2,2-dicyano-1-methylvinyl)-4-methylthiophene-3-carbonyl]amino}-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9b)

Orange crystals (from DMF), yield 81% (4.42 g), m.p. >300°C. IR (ν/cm^{-1}) = 3490–3330 (NH), 2973–2890 (CH_3, CH_2), 2225–2214 (4CN), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 7.01 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.12, 3.45 (2s, 6H, $2CH_3$), 4.22 (q, J = 7.01 Hz, 2H, CH_2), 6.56 (s, 1H, CH), 8.39 (s, br,

1H, NH, D_2O-exchangeable). $C_{27}H_{23}N_5O_4S_2$ (545.64): Calcd: C, 59.43; H, 4.25; N, 12.84; S, 11.75; Found: C, 59.19; H, 4.13; N, 12.74; S, 11.85.

General Procedure for the Synthesis of (10a,b)

To a solution of ethanolic sodium ethoxide [prepared by dissolving sodium metal (0.005 mol) in absolute ethanol (30 ml)] either **9a** or **9b** (0.005 mol) was added and the solution was heated in a boiling water bath for 8 h. The reaction mixture was then cooled, poured onto cold water, neutralized with dilute hydrochloric acid (pH 7) whereby the resulting solid product was filtered off, dried, and crystallized from the appropriate solvent.

2-(3,8-Diamino-4,7-dicyano-6-methyl-1-oxo-1H-benzo[4,5]thieno[3,2-c]pyridin-2-yl)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (10a)

Buff crystals (from AcOH), yield 60% (1.50 g), m.p. 261–263°C. IR (ν/cm^{-1}) = 3460–3320 ($2NH_2$), 2960–2875 (CH_3, CH_2), 2222–2215 (3CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 2.77 (s, 3H, CH_3), 4.91, 5.64 (2s, br, 4H, $2NH_2$, D_2O-exchangeable), 7.15 (s, 1H, CH). $C_{25}H_{18}N_6O_2S_2$ (498.58): Calcd: C, 60.22; H, 3.64; N, 16.86; S, 12.86; Found: C, 60.52; H, 3.54; N, 16.93; S, 12.83.

Ethyl 2-(3,8-Diamino-4,7-dicyano-6-methyl-1-oxo-1H-benzo[4,5]thieno[3,2-c]pyridin-2-yl)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (10b)

Pale brown crystals (from AcOH—H_2O), yield 57% (1.56 g), m.p. 233–234°C. IR (ν/cm^{-1}) = 3490–3330 ($2NH_2$), 2973–2890 (CH_3, CH_2), 2222, 2219 (2CN), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.54 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 2.77 (s, 3H, CH_3), 4.22 (q, J = 6.54 Hz, 2H, CH_2), 4.88, 5.49 (2s, br, 4H, $2NH_2$, D_2O-exchangeable), 7.15 (s, 1H, CH). $C_{27}H_{23}N_5O_4S_2$ (545.64): Calcd: C, 59.43; H, 4.25; N, 12.84; S, 11.75; Found: C, 59.59; H, 4.06; N, 12.74; S, 11.80.

General Procedure for the Synthesis of (14a,b)

A mixture of equimolar amounts (0.005 mol) of either **13a** or **13b** and elemental sulfur, in 1,4-dioxane (30 ml) containing a catalytic amount of triethylamine (0.5 ml), was boiled under reflux for 2 h. The solution was then poured over iced water and neutralized with dilute HCl to precipitate the solid products, which were filtered off, dried, and crystallized from the appropriate solvents.

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2-[(6-Amino-2-cyanomethylsulfanyl)thieno[3,4-b]thiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (14a)

Yellow crystals (from AcOH), yield 65% (1.54 g), m.p. 189°C. IR (ν/cm^{-1}) = 3460–3320 (NH, NH_2), 2960–2875 (CH_3, CH_2), 2222, 2219 (2CN), 1696, 1683 (2CO), 1640 (C=C). ^{1}H NMR δ = 1.66, 1.73 (2s, 6H, $2CH_3$), 2.68, 2.99 (2m, 4H, $2CH_2$), 3.94 (s, 2H, CH_2), 5.68 (s, 2H, NH_2, D_2O-exchangeable), 6.98 (s, 1H, CH), 9.43 (s, 1H, NH, D_2O-exchangeable). $C_{20}H_{16}N_4O_2S_4$ (472.63): Calcd: C, 50.82; H, 3.41; N, 11.85; S, 27.14; Found: C, 50.68; H, 3.47; N, 11.77; S, 27.29.

Ethyl 2-[(6-Amino-2-cyanomethylsulfanyl)thieno[3,4-b]-thiophene-3-carbonyl)amino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (14b)

Yellow crystals (from EtOH), yield 70% (1.82 g), m.p. 203–205°C. IR (ν/cm^{-1}) = 3490–3330 (NH, NH_2), 2973–2890 (CH_3, CH_2), 2222 (CN), 1705–1680 (3CO), 1630 (C=C). ^{1}H NMR δ = 1.15 (t, J = 6.22 Hz, 3H, CH_3), 1.69, 1.75 (2s, 6H, $2CH_3$), 2.70, 2.88 (2m, 4H, $2CH_2$), 3.94 (s, 2H, CH_2), 4.22 (q, J = 6.22 Hz, 2H, CH_2), 5.70 (s, 2H, NH_2, D_2O-exchangeable), 6.98 (s, 1H, CH), 9.05 (s, 1H, NH, D_2O-exchangeable). $C_{22}H_{21}N_3O_4S_4$ (519.68): Calcd: C, 50.85; H, 4.07; N, 8.09; S, 24.68; Found: C, 50.60; H, 4.11; N, 8.02; S, 24.52.

SCREENING FOR ANTIMICROBIAL ACTIVITY

Twelve compounds were screened *in vitro* for their antimicrobial activity against two bacterial isolates, one saprophytic (*Escherichia coli*) and the other is parasitic (*Xanthomonas citi*) and 3 fungal isolates one saprophytic (*Aspergillus fumigatus*) and two phytopathogenic (*Rhizoctonia solani* and *Fusarium oxysporum*). The culture medium was the nutrient agar for bacteria and Czapek's Dox agar medium for fungi. The sterile medium was inoculated with the test organism so that each 100 ml of the medium received 1 ml of a 24 hour culture of the bacterium or 7-day-old culture of spore suspension of the fungus. The solutions of the tested compounds at 25 μg/ml in dimethylformamide (DMF) were placed separately in the cup (8 mm diameter). The plates were incubated at 28°C and the resulting inhibition zones were measured. DMF as a blank exhibited no antimicrobial activity against any of the tested organisms used.

The recorded inhibition zones are summarized in Table I. The results indicated that most of the prepared compounds are active against the test organisms. The most toxic compounds against bacterial and fungal isolates were **10a**, **10b** and **5a** followed by **12a** and **8a**.

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TABLE I Inhibition Zones in mm for Some of the Synthesized Compounds at Concentration Level of 25 μg/ml

Compound	*E. coli*	*X. citri*	*A. fumigatus*	*R. solani*	*F. oxysporum*
5a	26	24	10	13	12
5b	21	17	7	7	6
7a	23	15	8	6	5
7b	19	11	0	0	0
8a	24	21	8	7	7
8b	18	18	0	0	0
10a	34	30	17	16	18
10b	29	26	14	14	13
12a	25	19	8	9	8
12b	22	16	6	5	4
14a	20	15	7	7	6
14b	17	10	6	6	5

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Compounds **7a**, **12b**, **14a** and **14b** were less toxic to the test organisms. The bacterial isolates were more susceptible to the synthesized compounds than fungal isolates. Compounds **7b** and **7b** were effective on bacterial isolates and did not exhibit any effect against fungal isolates. In conclusion, from the twelve compounds tested for antimicrobial screening, some showed encouraging activity. The compounds showing high activity were either thiophene or the annulated derivatives. Therefore, the present structures can be modified through studying the reactivity of the intermediate dipotassium disulphide salt **3** with other varieties of α-halocarbonyl compounds.

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