Synthesis of Some Novel 2-Anilinothiophene, 2,3′-Bithienyl and Thienylthiopyridine Derivatives Resistance to Penicillium Digitatum Effect the Fruit

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Reaction of benzotriazol-1-yl acetone **1** with phenyl isothiocyanate followed with α-chloroacetone or ethyl-α-chloroacetate afforded 2-anilinothiophenes **3** or **4**, respectively. Treatment of **3** with malononitrile at different reaction conditions afforded **6** or **7**. Reaction of **1** with CS_2 in DMF and phenacylbromide afforded *S*-alkylated thiophene **10**. Reactions of the latter compound with different active methylene nitriles afforded thienylthiopyridine derivatives **14** and **15**. Condensation of **10** with hydrazine hydrate afforded hydrazon derivative **16**. Reaction of thiophene **17** with formamide in DMF afforded **19** which converted to *N*-thienylpyrimidine **20** when treated with malononitrile. The structure of the newly synthesized compounds has been established on the basis of their analytical and spectral data. The compounds were also investigated for antibacterial and antifungal activities.

Keywords: Thiophenes; Bithienyl; Thienylthiopyridone; Pyrimidine.

INTRODUCTION

Pharmacological studies of thiophenes and their fused derivatives have been shown to possess a variety of pharmacological activities, such as in anticonvulsant agents[1] and antirheumatic drugs.[2] In fact, they are also known to be human GnRH receptor antagonists used to treat reproductive diseases[3] and have been used in the treatment of protozoal parasitic diseases.[4] Recently certain fused derivatives were prepared as anti-inflammatory agents, particularly for treating arthritis and as bone resorption inhibiting agents.[5] 4-Arylthiopyridine derivatives were prepared related to non-nucleoside RT inhibitors of HIV-1.[6] Promoted by these observations and in continuation of our interest in the design and synthesis of polyheterocyclic systems, particularly those containing a thiophene nucleus,[7-10] it was considered worthwhile to synthesize compounds bearing a thiophene nucleus linked directly to thiophene or to thieno-[2,3-b]pyridine, or to pyridine nuclei through an *S* linkage. Only a limited number of molecules where an *S* atom links pyridine to phenyl moieties has been described[6] in the literature but not to thienyl moieties. We undertook the synthesis of the title compounds which may show good biological, medical and agricultural applications.

RESULTS AND DISCUSSION

Treatment of benzotriazol-1-acetone **1** with phenyl isothiocyanate in *N,N*-dimethylformamide (DMF) containing potassium hydroxide afforded the insoluble intermediate salt **2**. The latter reacted *in situ* with an equimolar amount of different alkylating agents, namely α-chloroacetone or ethyl-α-chloroacetate, afforded in each case 2-anilinothiophene derivataives **3** or **4**, respectively, in good yield (Scheme I). The 5-acetyl-2-anilinothiophene **3** proved to be a useful key intermediate in the synthesis of several heterocyclic nuclei. Thus, when **3** was treated with an equimolar amount of malononitrile in ethanolic piperidine solution at a refluxed temperature, it afforded a single product **6**. The formation of the latter compound was considered to proceed *via* the intermediacy of Knovengel condensation **5** with spontaneous intramolecular cyclization *via* a Michael type electrophilic addition of its methyl group to the neighbouring CN group (Scheme I). Similar phenomena have been previously reported.[12-13]

In a continuation of our efforts to generate new synthetic routes to different polyfunctional thiophenes,[7-11] we have used Gewald's reaction[14] for the synthesis of 2,3′-bithienyl derivative **7**. The latter compound was obtained

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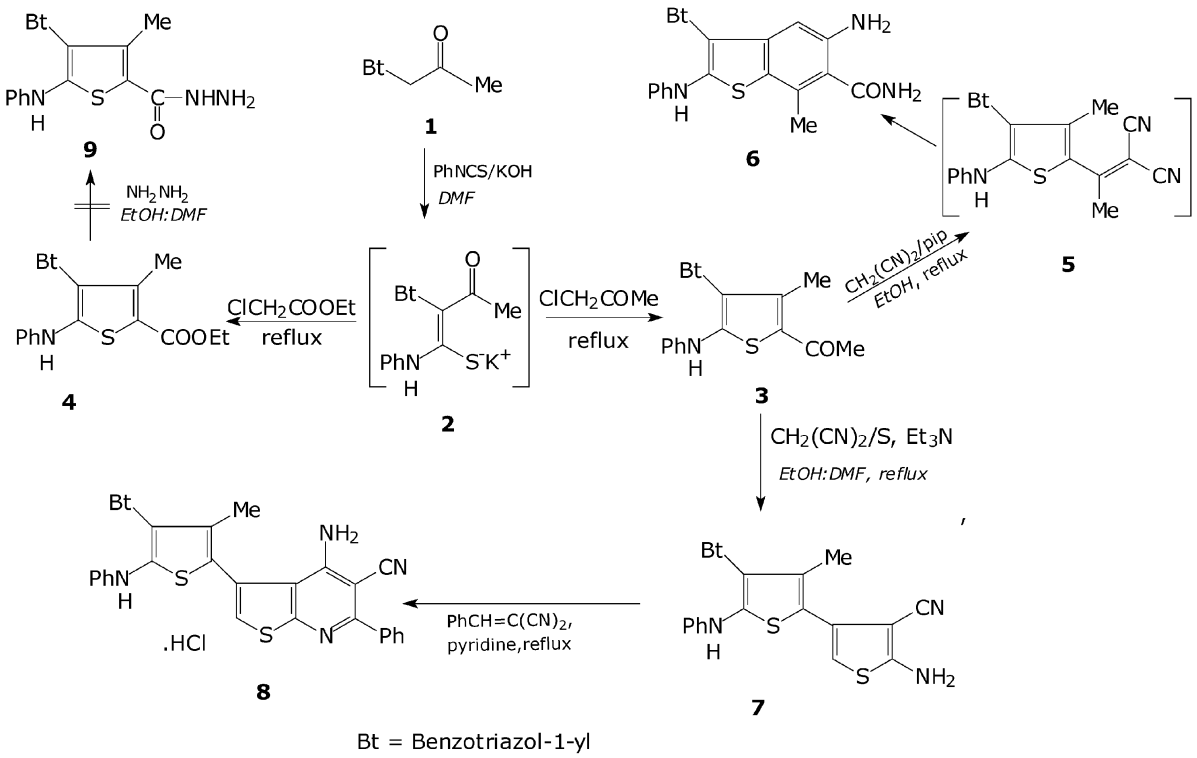
Scheme I



in situ via a one step process by treatment of **3** with malononitrile in the refluxing of ethanol and *N,N*-dimethylformamide mixture with the presence of elemental sulfur and a catalytic amount of triethylamine. The structure of **7** was established on the basis of elemental analysis and spectral data. Notably a literature survey revealed that polythiophenes appear to be good candidates due to their organic conducting polymers.[15]

The 2,3′-bithienyl derivative **7** underwent nucleophilic addition with benzylidenemalononitrile in refluxing pyridine to afford the thieno[2,3-b]pyridine derivatives **8** in good yield. The structure of **8** was confirmed on the basis of elemental analysis and spectral data. The formation of **8** is assumed to occur *via* initial formation of the Michael addition of the amino group in **7** to activate the double bond in benzylidenemalononitrile followed by intramolecular cyclization, then it loses hydrogen cyanide to afford the thieno[2,3-b]pyridine derivative **8**[9,11,16] (Scheme I).

Reaction of compound **4** with hydrazine hydrate in boiling ethanol and *N,N*-dimethylformamide mixture in an attempt to transform the ester group in compound **4** into acid hydrazide function **9** was unsuccessful; however, again the ^{1}H NMR spectrum of the reaction product was found to have an ethyl group as triplet and quartet at δ_H 1.25 and 4.26 ppm with $J = 7$ Hz (Scheme I).

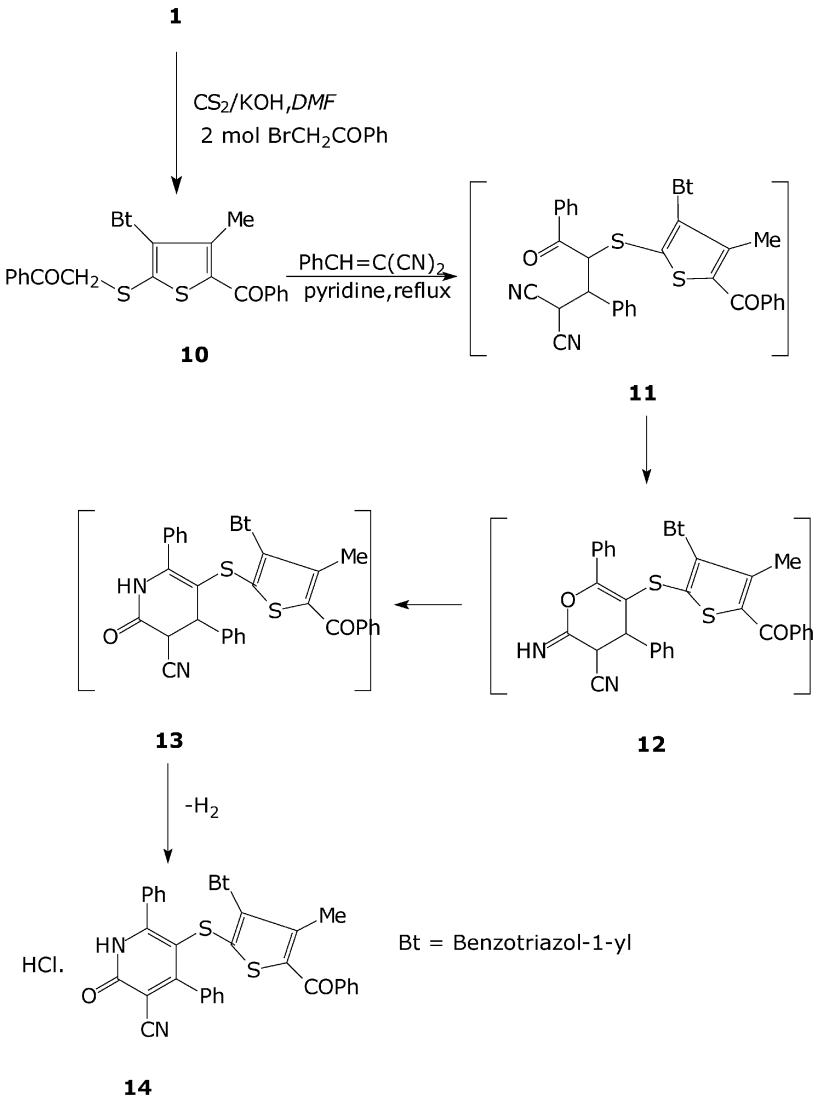
On the other hand, treatment of **1** with carbon disulfide in *N,N*-dimethylformamide solution (DMF) containing potassium hydroxide and subsequent treatment of the reaction mixture with two molar amount of phenacylbromide *in situ* afforded the *S*-alkylated thiophene **10**. The ^{13}C NMR data of **10** shows two low field signals at δ_C 189 and 194 ppm. The signal at approx. δ_C 189 corresponds to the conjugated carbonyl carbon (CO) while that at δ_C 194 corresponds to carbonyl carbon bonded to methylene group (*S*CH_2CO); in addition, the high field signal δ 45 ppm corresponds to the *S*CH_2 group. The activated methylene group in **10** readily takes part in numerous reactions providing more complex molecules. Reaction of **10** with benzylidenemalononitrile in refluxing pyridine afforded **14**. The formation of **14** is assumed to take place *via* the initial Michael addition of active methylene of **10** to an activated double bond in benzylidenemalononitrile yielding **11** that then subsequently cyclizes to **12**. The latter intermediate undergoes Dimorth type rearrangement to **13** which aro-

matizes to **14** *via* loss of a hydrogen molecule. The ^{13}C NMR data of compound **14** shows two signals at approx. δ_C 150 and δ_C 188 ppm corresponding to the amide carbonyl and conjugated carbonyl carbon, respectively, while the signal corresponding to the methylene group was not observed (Scheme II).

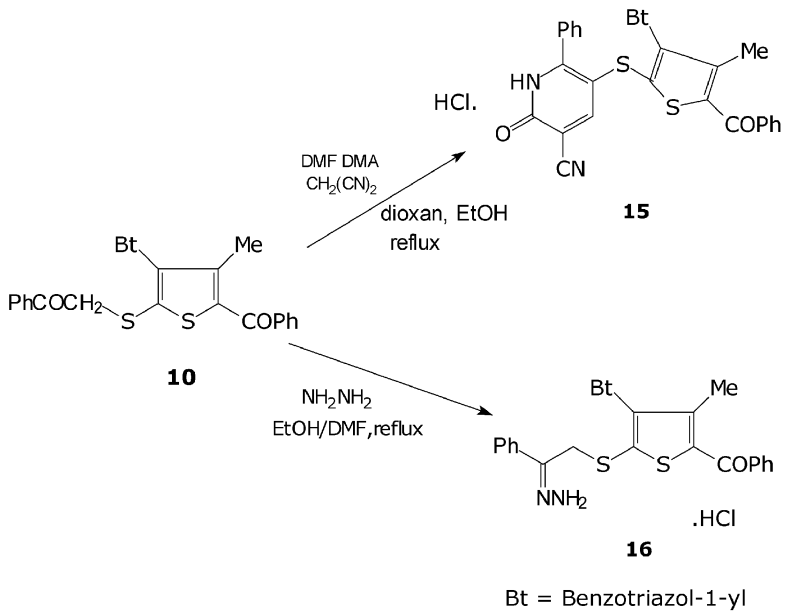
Condensation of **10** with *N,N*-dimethylformamide dimethylacetal (DMF DMA) in refluxing dioxan and then subsequent treatment of the reaction mixture *in situ* with malononitrile afforded the pyridine derivative **15**. The structure of **15** was established on the basis of its elemental analysis and spectral data. For example, the ^1H NMR showed a resonance at approximately 8.15 ppm corresponding to H-4 of the pyridine ring. Moreover, the ^{13}C NMR spectrum of the reaction product revealed two low field signals at δ_C 145 and 188.6 ppm corresponding to amide carbonyl and conjugated carbonyl carbon, respectively. Treatment of compound **10** with hydrazine hydrate in a mixture of ethanol and *N,N*-dimethylformamide at reflux temperature afforded 2′-hydrazon derivative **16** (Scheme III).

Compound **17** was readily prepared according to a recently described procedure.[11] Treatment of the latter compound with formamide in refluxing *N,N*-dimethylformamide (DMF) produce either 4-aminothieno[2,3-d]pyrimidine **18** or **19**. In fact, only a single product was obtained; structure **18** was ruled out on the basis of its elemental anal-

Scheme II

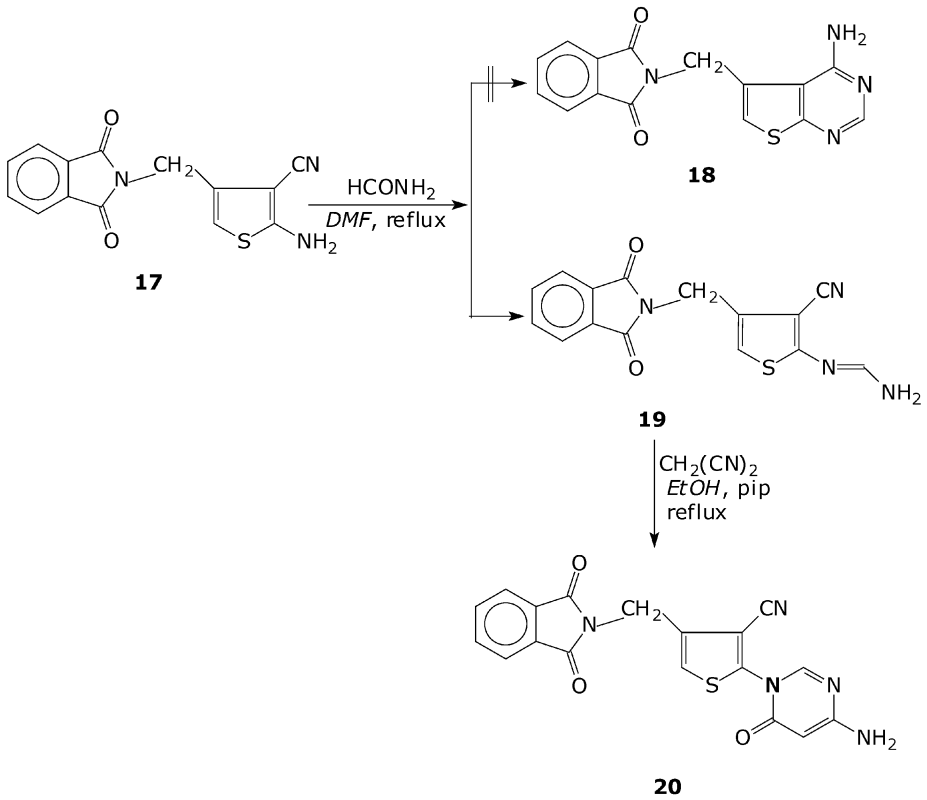


Scheme III



Bt = Benzotriazol-1-yl

Scheme IV



ysis and spectral data. The presence of the cyano group absorption in the IR spectrum of the product indicates that the cycano group is not involved in the reaction (Scheme IV).

Treatment of compound **19** with malononitrile in refluxing ethanol and in the presence of a catylatic amount of piperidine gave 3-thien-2-yl-pyrimidine derivative **20**.

Table 1. In *vitro* bactericidal and fungicidal activities of newly synthesized compounds

Compound	*B-subtilis*	*E-colic*	*P-digitalum*	*A-niger*
6	++	++	++	+
7	+	+	++	-
10	++	-	++	-
15	-	-	+++	-
16	-	-	-	-
20	-	-	+	-

Slight effect = +; Moderate effect = ++; Strong effect = +++

BIOLOGICAL ACTIVITY

The biological activities of some of the newly synthesized compounds were screened for antifungal activity against *Aspergillus niger* and *Penicillium digitatum* while the antibacterial activity was tested against *Escherichia coli* and *Bacillus subtilis*. Most of the test samples showed bacterial and fungicidal activity (Table 1), especially to the fungus *Penicillium digitatum* which affect fruit. These fungus cause decay in fruit and then it becomes soft and shrinks.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in dimethyl-d_6-sulfoxide as solvent and tetramethylsilane *TMS* as internal standard; chemical shifts are reported as δ units (ppm). Mass spectra were measured on GS/MS VG Autospec Q instrument. Microanalyses were performed on a LECO CHNS 932 analyzer. Compound **17** was prepared according to the literature.[11]

Reaction of 1-Benzotriazolylacetone with α-Chloroacetone or Ethyl α-Chloroacetate (3-4)

General Procedure

A solution of **1** (1.75 g, 10 mmol), phenyl isothiocyanate (1.35 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) in DMF (20 mL) was stirred for 8 h at room temperature. To a stirred solution, either α-chloroacetone or ethyl-α-chloroacetate (10 mmol) was added and refluxed for 3 h. The reaction mixture was allowed to cool at room temperature, then poured into ice-cold water and neutralized with HCl (10%). The solid product so formed was collected by filtration and recrystallized from the proper solvent.

5-Acetyl-2-anilino-3-benzotriazol-1-yl-4-methylthiophene (3)

This compound was recrystallized from EtOH as brown crystals, 2.86 g (83%), mp. 157-159 °C, IR: ν = 3274 (NH), 1633 (keto CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H 1.97 (s, 3H, CH_3), 2.15 (s, 3H, $COCH_3$), 7.04-8.20 (m, 9H, Ar-H), 9.25 ppm (br.s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ_C 19.6 (CH_3), 30.1 ($COCH_3$), 111.3, 116.8, 119.4, 120.7, 124.7, 125.7, 126.2, 129.5, 130.4, 135.2, 142.3, 146.0, 151.9, 152.8 (aromatic carbons) 190.1 ppm (keto CO). Anal. Calcd. for $C_{19}H_{16}N_4OS$ (348.35): C, 65.51; H, 4.63; N, 16.08; S, 9.20%. Found: C, 65.37; H, 4.75; N, 16.05, S, 9.10.

Ethyl-2-anilino-3-benzotriazol-1-yl-4-methylthiophene-5-carboxylate (4)

This compound was recrystallized from EtOH as yellow crystals, 2.5 g (67%) mp. 146-148 °C. IR: ν = 3239 (NH), 1702 (ester CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H 1.25 (t, 3H, J = 7 Hz, CH_3), 2.01 (s, 3H, CH_3), 4.26 (q, 2H, J = 7 Hz, CH_2), 7.01-8.17 (m, 9H, Ar-H), 9.18 ppm (br.s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{18}N_4O_2S$ (378.38): C, 63.48; H, 4.80; N, 14.81%. Found: C, 63.45; H, 4.67; N, 14.88.

6-Acetamido-5-amino-2-anilino-3-benzotriazol-1-yl-7-methyl benzo[b]thiophene (6)

To a stirred solution of **3** (3.48 g, 10 mmol) in EtOH (20 mL) were added malononitrile (0.66 g, 10 mmol) and a few drops of piperidine. The reaction mixture was refluxed for 2 h, then left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from EtOH as off-white crystals, 2.73 g (66%), mp. 170-172 °C. IR: ν = 3448-3179 ($2NH_2$ & NH), 1588 (amide CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H 2.36 (s, 3H, CH_3), 5.20 (br.s, 2H, NH_2 D_2O exchangeable), 7.26-8.17 (m, 10H, Ar-H), 10.69 (br.s, 2H, NH_2, D_2O exchangeable), 12.35 ppm (br.s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ_C 20.44 (CH_3), 110.7, 111.2, 113.6, 120.3, 120.7, 124.1, 125.2, 127.5, 127.9, 128.1, 128.6, 129.6, 129.8, 129.9, 136.0, 139.2, 139.8, 146.4 (aromatic carbons), 174.9 ppm (amide CO). Anal. Calcd. for $C_{22}H_{18}N_6OS$ (414.41): C, 63.76; H, 4.38; N, 20.38%. Found: C, 63.48; H, 4.65; N,

20.12.

2-(5′-Amino-4′-cyanothien-3′-yl)-5-anilino-4-benzotriazol-1-yl-3-methylthiophene (7)

A solution of **3** (3.48 g, 10 mmol), malononitrite (0.66 g, 10 mmol) and the element sulfur (0.32 g, 10 mmol) in a mixture of EtOH : DMF (2:1, v/v) containing Et_3N (1.0 mL) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from EtOH : DMF (2:1, v/v) as brown crystals, 240 g (69%), mp. 194-201°C. IR: ν = 3266-3435 (NH_2 & NH), 2209 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 1.97 (s, 3H, CH_3), 6.99 (s, 1H, H-2′, thienyl-H), 7.17-8.18 (m, 9H, Ar-H), 8.20 (br s, 2H, NH_2, D_2O exchangeable), 9.25 ppm (br s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ_C 14.7 (CH_3), 111.2, 116.7, 119.4, 120.7, 120.3, 120.5, 120.6, 121.1, 124.7, 125.5, 128.3, 129.7, 130.4, 130.5, 141.8, 142.5, 144.9, 145.9, 153.13 ppm (aromatic carbons). Anal. Calcd. for $C_{22}H_{16}N_6S_2$ (428.40): C, 61.68; H, 3.76; N, 19.62%. Found: C, 61.88; H, 3.91; N, 19.92.

4-Amino-3-(5′-anilino-4′-benzotriazol-1-yl-3′-methylthion-2′-yl)-5-cyano-6-phenylthieno[b]pyridine hydrochloride (8)

A mixture of **7** (3.48 g, 10 mmol) and benzylidenemalononitrile (1.54 g, 10 mmol) in pyridine (20 mL) was refluxed for 3 h. The reaction mixture was then allowed to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from EtOH : DMF (2:1, v/v) as brown crystals, 3.11 g (71%) mp. 188-190 °C. IR: ν = 3264-3435 (NH_2 & NH), 2209 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 1.97 (s, 3H, CH_3), 7.03 (s, 1H, H-2, thienyl-H), 7.20-8.14 (m, 14H, Ar-H), 8.20 (br.s, 2H, NH_2 D_2O exchangeable), 9.25 ppm (br.s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6); δ_C 15.4 (CH_3), 111.4, 116.8, 120.2, 120.5, 120.6, 120.7, 121.2, 123.2, 125.2, 125.4, 125.5, 129.4, 129.5, 129.6, 130.0, 130.1, 130.5, 132.1, 135.2, 135.5, 135.6, 141.1, 142.3, 146.0, 148.0, 152.8 ppm (aromatic carbons). Anal. Calcd. for $C_{31}H_{22}N_7S_2Cl$ (591.98): C, 62.89; H, 3.74; N, 16.56; S, 10.81%. Found: C, 63.19; H, 4.05; N, 16.65; S, 10.73.

3′-Benzotriazol-1-yl-5′-benzoyl-4′-methylthien-2′-ylthioacetophenone (10)

A solution of **1** (1.75 g, 10 mmol), carbon disulfide (0.76 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) in DMF (20 mL) was stirred for 10 h at room temperature. To the stirred solution, phenacylbromide (0.98 g, 20 mmol) was added, then refluxed for 6 h. The reaction mixture was allowed to cool at room temperature, then neutralized with HCl (10%). The solid product so formed was collected by filtration and recrystallized from EtOH: DMF (2:1, v/v) as brown crystals 3.71 g (82%), mp. 75-77 °C. IR: ν = 1679 ($COCH_2$), 1639 (COPh) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 1.94 (s, 3H, CH_3), 4.85 (s, 2H, SCH_2), 7.40-8.21 ppm (m, 14H, benzotriazolyl & phenyl-H). ^{13}C NMR (DMSO-d_6): δ_C 15.2 (CH_3), 44.7 (CH_2), 111.6, 120.82, 125.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 129.9, 130.0, 130.4, 130.5, 133.9, 134.2, 135.0, 139.5, 145.8 (aromatic carbons), 188.7 (COPh), 194.2 ppm ($COCH_2$). Anal. Calcd for $C_{26}H_{19}N_3O_2S_2$ (469.45): C, 66.52; H, 4.07; N, 8.95; S, 13.60%. Found: C, 66.33; H, 4.31; N, 9.04; S, 13.50.

3-Cyano-1,2-dihydro-2-oxo-4,6-diphenyl-5-thio-[3′-benzotriazol-1-yl-5′-benzoyl-4-methylthien-2′-yl]pyridine hydrochloride (14)

To a stirred solution of **10** (4.71 g, 10 mmol) in pyridine (20 mL), benzylidenemalononitrile (1.54 g, 10 mmol) was added and refluxed for 5 h. The reaction mixture was allowed to cool at room temperature, then poured into ice-cold water and neutralized with HCl (10%). The precipitate was collected by filtration and recrystallized from DMF : EtOH (1:2, v/v) as brown crystals, 4.07 g (62%), mp. 112-114 °C. IR: ν = 3365 (NH), 2224 (CN), 1642 (keto CO), 1593 (amide CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 1.94 (s, 3H, CH_3), 8.20 (br.s, 1H, NH D_2O exchangeable), 7.48-7.87 ppm (m, 19H, benzotriazolyl & phenyl-H). ^{13}C NMR (DMSO-d_6): δ_H 19.5 (CH_3), 115.8, 115.9, 125.4, 127.8, 129.1, 130.5, 130.6, 131.9, 133.2, 133.5, 133.8, 134.4, 134.6, 135.2, 136.9, 137.7, 137.8, 138.4, 138.8, 138.9, 140.1, 141.9, 143.4, 143.6, 146.2, 148.3, 148.5 (aromatic carbons & CN), 150.2 (amide CO), 188.0 ppm (keto CO). Anal. Calcd. for $C_{36}H_{24}N_5O_2S_2Cl$ (657.82): C, 65.73; H, 3.67; N, 10.62%. Found: C, 65.85; H, 3.77; N, 10.72.

3-Cyano-1,2-dihydro-2-oxo-6-phenyl-5-thio(3′-benzotriazol-1-yl-5′-benzoyl-4′-methylthien-2′-yl]pyridine hydrochloride (15)

To a stirred solution of **10** (4.71 g, 10 mmol) in dioxan (20 mL), DMF DMA (1.33 g, 10 mmol) was added. The reaction mixture was refluxed for 3 h, then left to cool at room temperature. To the refluxed mixture, a solution of

malononitrile (0.66 g, 10 mmol) in EtOH (20 mL) containing piperidine (1.0 mL) was added. The reaction mixture was refluxed for 2 h, then allowed to cool at room temperature and poured into ice cold water. The solid product so formed was collected by filtration and recrystallized from EtOH as brown crystals, 4.01 g, (69%); mp. 90-92 °C, IR: ν = 3319 (NH), 2200 (CN), 1639 (keto CO) and 1596 (amide CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 1.97 (s, 3H, CH_3), 7.46-8.10 (m, 14H, Ar-H), 8.15 (s, 1H, H-4, pyridine-H), 8.22 ppm (br.s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ_C 18.7 (CH_3), 111.2, 111.5, 120.8, 125.9, 127.8, 128.9, 129.4, 129.6, 129.8, 130.1, 130.3, 130.4, 132.0, 133.7, 133.9, 134.3, 134.6, 135.5, 137.6, 138.8, 139.0, 141.7, 143.1 (aromatic carbons), 145.7 (amide CO), 188.6 ppm (keto CO). Anal. Calcd. for $C_{30}H_{20}N_5S_2O_2Cl$ (581.96): C, 61.91; H, 3.46; N, 12.03%. Found: C, 62.03; H, 3.60; N, 12.09.

3-Benzotriazol-1-yl-5-benzoyl-4-methyl-2-thio(ethyl-2′-hydrazono-2′-phenyl)thiophene hydrochloride (16)

To a stirred solution of **10** (4.71 g, 10 mmol) in a mixture of EtOH : DMF (1:1, v/v), hydrazine hydrate (0.5 g, 10 mmol) was added. The reaction mixture was refluxed for 1 h, then allowed to cool at room temperature and neutralized with HCl (10%). The precipitate was collected by filtration and recrystallized from EtOH:DMF (2:1, v/v) as brown crystals, 3.68 g (71%), mp. 102-104 °C. IR: 3314-3434 (NH_2), 1645 (keto CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H 2.0 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 7.28-7.90 ppm (m, 14H, Ar-H), 8.12 (br.s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ_C 15.2 (CH_3), 31.8 (CH_2), 111.2, 111.6, 120.8, 125.8, 127.8, 129.2, 129.3, 129.4, 129.8, 130.0, 130.1, 130.3, 134.2, 134.4, 136.4, 139.1, 141.8, 145.6 (aromatic carbons), 163.3 (C=NNH_2), 188.0 ppm (keto CO). Anal. Calcd. For $C_{26}H_{22}N_5OS_2Cl$ (519.93): C, 60.06; H, 4.26; N, 13.46%. Found: C, 60.09; H, 4.21; N, 13.46.

2-(Aminomethylenimino)-4-(phthalimidomethyl)-3-cyanothiophene (19)

A mixture of **17** (2.83 g, 10 mmol) and formamide (0.39 g, 10 mmol) in DMF (20 mL) was refluxed for 10 h. The reaction was left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from DMF : EtOH (2:1 v/v) as brown crystals, 2.01 g (65%), mp. 138-140 °C. IR: ν = 3312-3394 (NH_2), 2204 (CN), 1772, 1718 cm^{-1} (phthalmide CO). ^1H NMR (DMSO-d_6): δ_H 4.88 (s, 2H, CH_2N), 7.20 (s, 1H, H-5, thiophene-H), 7.28-7.95 (m, 5H, phthalimide-H & methylenic-H), 8.03 ppm (br.s, 2H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{10}N_4O_2S$ (310.26): C, 58.06; H, 3.24; N, 18.04%. Found: C, 58.03; H, 3.52; N, 17.85.

6-Amino-3-(3′-cyano-4′-phthalimidomethylthien-2′-yl)-3,4-dihydro-4-oxopyrimidine (20)

A mixture of **19** (3.20 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in EtOH (20 mL) containing a few drops of piperidine was refluxed for 2 h. The solid product so formed was collected by filtration and recrystallized from EtOH : DMF (2:1 v/v) as brown crystals, 2.60 g (69%); mp. 190-192 °C. IR: ν = 3323-3198 (NH_2), 2208 (CN), 1772 and 1716 (phthalimide CO), 1635 cm^{-1} (amide CO). ^1H NMR (DMSO-d_6): 4.79 (s, 2H, CH_2), 7.23 (s, 1H, H-5, thienyl-H), 7.68-8.36 (m, 8H, Ar-H & NH_2). ^{13}C NMR (DMSO-d_6): δ_C 41.7 (CH_2N); 115.9, 117.0, 124.4, 124.6, 132.6, 134.5, 135.1, 135.6, 136.0, 146.7, 154.0 (aromatic carbons), 164.9 (amide CO), 168.4 ppm (phthalimide CO). Anal. Calcd. for $C_{18}H_{11}N_5O_3S$ (377.31): C, 57.29; H, 2.93; N, 18.56%. Found: C, 57.28; H, 3.01; N, 18.41.

BIOLOGICAL TESTING

The newly synthesized compounds were tested against the specified microorganism using 400 μg/mL (w/v) solutions in sterile dimethyl-d_6-sulfoxide (DMSO). A solution of the tested compound (1.0 mL) was poured aseptically in a well of 6 mm diameter made by a Cork borer in the nutrient agar (NA) medium for the bacterial test and Sabouraud's agar for the fungal test. After placing the same volume in wells of all tested microorganisms, nutrient agar plates were incubated at 37 °C for 48 h, and Sabouraud's dextrose agar (SDA) plates were incubated at 25 °C for 48 h. The activities were expressed as inhibition zones (mm, diameter, as clear areas) as antibacterial and antifungal effects. The least concentration, which showed inhibitory effect on any specific microorganism, was considered as the minimum inhibitory concentration (MIC) which was determined using streptomycin (50 μg/mL) as the reference.

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REFERENCES

1. Amer, A. A.; Hegab, M.; Ibrahim, A. A.; Abdulla M. *Manatschefte fur Chemie* **2003**, *134*, 1395.
2. Baba, A.; Mori, A.; Yasuma, T.; Unno, S.; Makino, H.; Sohda, T. *Chem. Pharm. Bull*. **1999**, *47*(7), 993.
3. Cuo, Z.; Chen, Y.; Wu, D.; Zhu. Y.; Strulher, R.; Saunders, J.; Xie, Q.; Chen, C. *Bioinorg. Medicinal. Chem. Lett.* **2003**, *13*, 3617.
4. Valderama, J.; Fournet, A.; Valderrama, C.; Bastias, S.; Asludillo, C.; De Arias, A.; Inchausti, A.; Yaluff, G. *Chem. Pharm. Bull* **1999**, *47*(9), 1221.
5. Sohda, T.; Makino, H.; Baba, A. *PCT Int. Appl. WO* **1996**, *14*, 319; *Chem. Abstr*. **1996**, *125*, 114583x.
6. Dolle, V.; Aubertin, A. M.; Ludwig, O.; Nguyen, C. H.; Bisagni, E.; Legraverend, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*(2), 173.
7. Al-Omran, F. *Sulfur Lett.* **2000**, *23*(6), 275.
8. Mohareb, R. M.; Al-Omran, F.; Ho, J. Z. *Monatshefte fur Chemie* **2002**, 1443.
9. Al-Omran, F.; Mohareb, R. M.; El-Khair, A. A. *J. Heterocycl. Chem*. **2002**, *39*, 877.
10. Mohareb, R. M.; Al-Omran, F.; Ho, J. Z. *J. Heteroat. Chem*. **2001**, *2*, 168.
11. Al-Omran, F.; El-Khair, A. A. *J. Heterocycl. Chem*. **2004**, *41*, 909.
12. Yamanak, H.; Oh, S.; Konno, S. *J. Heterocycles* **1987**, *26*, 2583.
13. Sherif, S. A.; Wardakehan, W.; Mohareb, S. M. *J. Chem. Res.(S)* **1996**, 356; *J. Chem. Res.(M)* **1996**, 1.
14. Gewald, K.; Schinke, *E. Chem. Ber.* **1996**, *99*, 94.
15. Sabnis, R. W.; Rangnekar, D. W.; Sonawana, N. D. *J. Heterocycl. Chem*. **1996**, *36*, 333.
16. El-Khandeel, K. *Heteroat. Chem*. **1996**, *7*, 29.