Synthesis of Polyfunctionally Substituted Heteroaromatic Compounds *via* Benzotriazolyl Chalcones with Antimicrobial and Antifungal Activities

Fatima Al-Omran* and Adel Abou El-Khair

Chemistry Department, Faculty of Science, Kuwait University
P.O. Box 5969, 13060 Safat, Kuwait
Received November 20, 2003

The utility of both 3-(1-benzotriazolyl) chalcone derivatives **3a-c** and 2-(1-benzotriazolyl)-1,4-pentadien-3-one (**18**) in the synthesis of some new 2-(1*H*)-pyridone, pyridine, pyrazole and isoxazole derivatives is reported. Antimicrobial and antifungal screening of some selected examples from the synthesized products were carried out. The structure of the newly synthesized compounds was elucidated by elemental analysis, ir, ^{1}H and ^{13}C nmr investigations.

J. Heterocyclic Chem., **41**, 327 (2004).

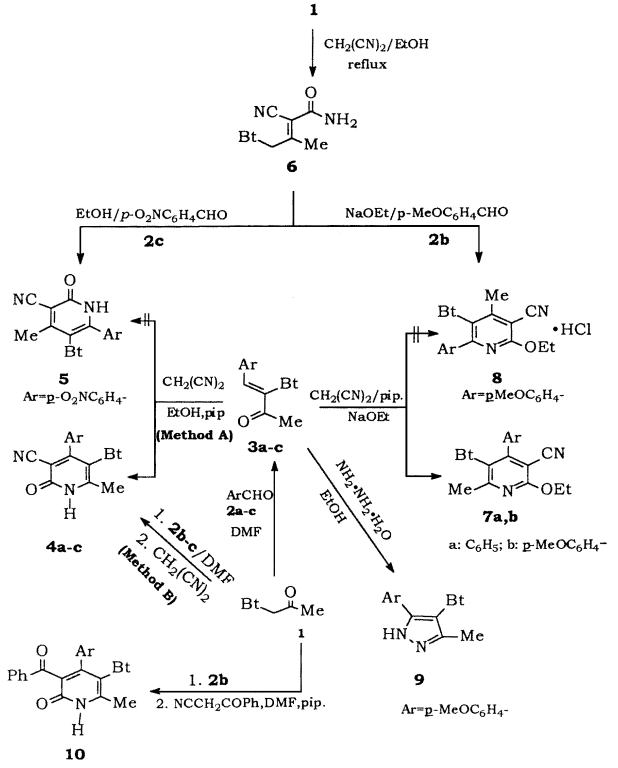
The increasing importance of both chalcone and benzotriazole derivatives as intermediates to biologically active compounds [1-7] and in continuation of our current interest in the synthesis of polysubstituted heterocycles incorporating benzotraizole moiety as potential pharmaceuticals [8-11], we reported here on the utility of unreported 3-(1-benzotriazolyl) chalcone derivatives **3a-c** and 2-(1-benzotriazolyl)-1,4-pentadien-3-one derivative **18** as building blocks for synthesis of new polyfunctionally substituted heteroaromatic compounds of expected potential antimicrobial and antifungal activities.

Thus, refluxing an equimolar amount of 1-(1-benzotriazolyl)acetone **1** with aromatic aldehydes **2a-c** in dimethylformamide (DMF) and in the presence of a catalytic amount of triethylamine afforded in each case of 3-(1-benzotriazolyl) chalcones **3a-c** in good yield. The reactivity of the new chalcones **3a-c** obtained was investigated toward carbon nucleophiles. Treatment of compounds **3a-c** with malononitrile in ethanolic piperidine solution at refluxed temperature (Method A), furnished in each case, one isolable product that could be formulated as 2-(1*H*)-pyridone **4** or its isomer **5**. The compound **5** was obtained by an independent synthetic route *via* treatment of **1** with malononitrile in refluxing ethanol to afforded product **6**. The latter compound was treated with **2c** to afford a deep brown product identified as 5-(1-benzotriazolyl)-4-methyl-6-(*p*-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**5**) with different melting point than the product obtained from reaction of **3c** with malononitrile but with similar spectral data. The compounds **4c-d** could be obtained in situ, *via* a one step process by treatment of **1** with *p*-methoxybenzaldehyde (**2b**) or *p*-nitrobenzaldehyde (**2c**) in refluxing DMF followed by treatment of the reaction mixture with malononitrile (Method B) to afford a product identical in all respects (mp and spectra) with that obtained from the reaction of compounds **3b-c** with malononitrile. The formation of **4** was assumed to proceed *via* initial addition of active methylene reagent across the double bond in **3c** followed by hydrolysis of one of the cyano groups and then cyclization to **4**.

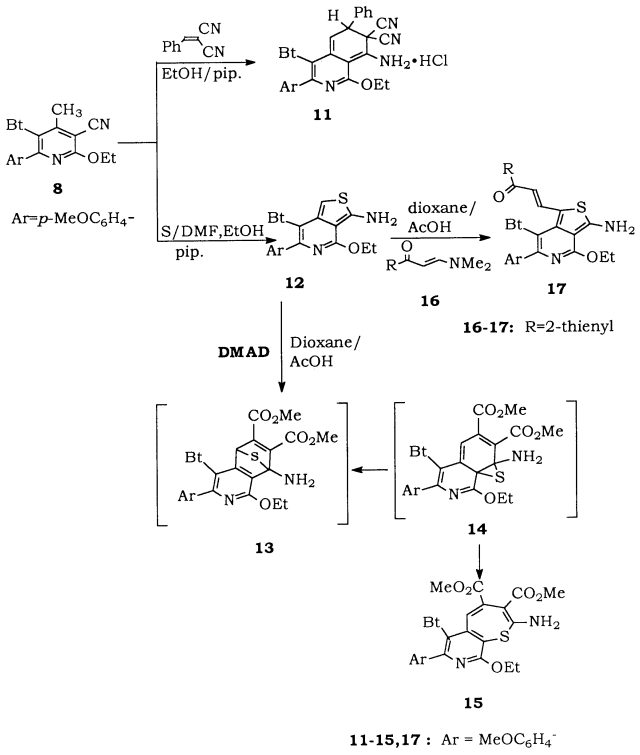
In a similar manner, treatment of chalcones **3a,b** with malononitrile in ethanolic sodium ethoxide and in the presence of a catalytic amount of piperidine at refluxed temperature gave a product that could be formulated as **7** or its isomer **8**. Spectral data seemed to be little help in discriminating **7** or **8**. However, the structure **8** was ruled out on the basis of the reaction **6** with *p*-methoxybenzaldehyde (**2b**) in ethanolic sodium ethoxide at refluxed temperature to afford a product with different melting point than the product obtained previously from the reaction of **3b** with malononitrile in ethanolic sodium ethoxide. Compound **7** was assumed to proceed *via* initial addition of the carbanion of malononitrile across the activated double bond system in **3b** followed by the addition of ethoxide ion to one of the cyano groups to the iminoether, which readily undergoes cyclization *via* a nucleophilic attack of an NH group on a carbonyl carbon. This sequence of events has been recently suggested to account the formation of alkoxy pyridine [10,12].

The reactivity of chalcone **3b** towards nitrogen nucleophile was also investigated. Thus, treatment of compound **3b** with hydrazine hydrate in refluxing ethanol afforded yellow crystals that were identified as a pyrazolylbenzotriazole (Scheme 1). The formation of **9** is assumed to proceed *via* condensation of hydrazine with the carbonyl group in chalcone and subsequent cyclisation into the pyrazole derivative **9**. This is similar to the well accepted mechanism of the reaction of chalcones with nitrogen nucleophile [13]. Treatment of 1-(1-benzotriazolyl)-acetone **1** with *p*-methoxybenzaldehyde (**2 b**) followed by treatment of the reaction mixture with benzoylacetonitrile in refluxing DMF and piperidine afforded **10**. The structure of **10** was established on the basis of its elemental analysis and spectral data. Thus, the ir spectrum of the reaction product shows the NH and two carbonyl functions (ketone and amide) at ν_{max} 3652, 1692 and 1650 cm^{-1}, respectively (Scheme 1).

Scheme 1



Scheme 2



2a-c - 4a-c: Ar= a: C_6H_5; b: *p*-$MeOC_6H_4$- ; c: *p*-$O_2NC_6H_4$-; Bt=1-Benzotriazolyl

Treatment of **8** with each of benzylidenemalononitrile or by refluxing it in a mixture of DMF/ethanol in the presence of elemental sulfur and a catalytic amount of piperidine gave compounds **11** and **12**, respectively in good yield [14-16]. Treatment of **12** with dimethyl acetylenedicarboxylate (DMAD) afforded the thiepine derivative **15**, which is believed to be formed *via* the non-isolated intermediates **13** and **14** (*cf.* Scheme 2). Similar formation of theipins has been reported from our laboratorie [15-17] as well as by Dopp *et al* [18]. The structure of the isolated product **15** was confirmed on the basis of elemental analysis and spectral data. On the other hand, treatment of compound **12** with enaminone **16** in refluxing dioxane and in the presence of a catalytic amount of acetic acid afforded only the C-1 alkylated product **17** in a good yield. Both the ir and ^{1}H nmr spectra indicated that the amino function was not involved in the reaction. The ^{1}H nmr spectrum indicated the presence of two *trans* vinylic protons at δ_H = 5.85 and 6.39 ppm with J = 15 Hz. Thus, structure **17** was established as the reaction product, which was similar to the well accepted reaction of condensed thiophenes with enaminones, reported from our laboratories [16,19] (*cf.* Scheme 2).

Furthermore, treatment of 1-(1-benzotriazolyl)acetone **1** with an excess of *p*-nitrophenylbenzaldehyde (**2c**) in DMF and in presence of a catalytic amount of triethylamine at reflux temperature afforded the dienone **18** in excellent yield. The products structure was established on the basis of its elemental analysis and spectral data (Scheme 3). The reactivity of compound **18** towards some nitrogen and carbon nucleophilies was also investigated.

Thus, treatment of **18** with hydrazine hydrate or hydroxyl amine in ethanol afforded in each case a product that formulated as pyrazolylbenzotriazole and isoxazolylbenzotriazole derivatives **19** and **20**, respectively. The formation of **19** and **20** is assumed to proceed *via* initial addition of hydrazine or hydroxylamine to the carbonyl group in system **18** and the resulting product then cyclises into the pyrazole or isoxazole derivatives **19** and **20** respectively [13].

On other hand, treatment of **18** with malononitrile or benzoylacetonitrile in refluxing ethanolic piperidine afforded the 2-(1*H*)-pyridinone derivatives **21** and **22**, respectively in good yield. Both elemental analysis and spectral data were in complete agreement with the assigned structures. The structure **21** and **22** are considered most likely for the products based on its similarity to the well established behaviour, which was assumed to proceed *via* initial addition of active methylene reagent across the activated double bond system in dienone **18** followed by hydrolysis and cyclization *via* loss of water a molecule [12].

In a similar manner, dienone **18** reacted with malononitrile in refluxing ethanolic sodium ethoxide to give the

product that was established as 2-ethoxypyridine 3-carbonitrile derivative **23** in good yield. The ir spectrum of compound **23** showed a characteristic absorption band at 2191 cm^{-1} due to the nitrile function. The structure may be formed *via* initial addition of the carbanion of malononitrile across the activated double bond system in dienone **18** followed by addition of ethoxide ion to one of the cyano groups which subsequently cyclises *via* loss of water to afford 2-ethoxypyridine-3-carbonitrile derivative **23** (Scheme 3) [12].

Scheme 3

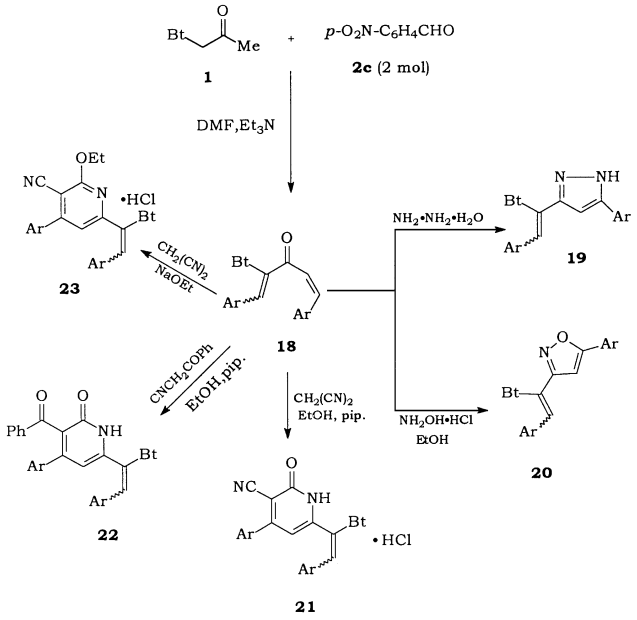


Table 1

In *vitro* Bactericidal and Fungicidal Activity of Newly Synthesized Compounds

Compound	*E-coli*	*B-subtilis*	*S-aureus*	*A-niger*	*F-oxysporium*
3c	++++	++	+++	+++	+++
7b	++++	+++	++++	+++	+++
10	++	-	+++	+++	+++
11	+++	++	++++	+++	+++
12	++++	+++	+++	+++	+++
15	++++	+++	++++	+++	+++
17	+++	+++	+++	+++	+++
18	+++	++	+++	-	+++
20	+++	++	++	-	+++
22	+++	-	-	++	+++

No effect = - ; slight effect = + ; Moderate effect = ++ ; strong effect = +++, ++++

Biological Activity.

The biological activities of some newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger* and *Fusarium oxysporium*, while the antibacterial activity was tested against *Eschirichia coli, Bacillus subtilis* and *Staphylococcus aureus*. Most of the tested sample showed strong antibacterial and fungicidal activity (Table 1). Bacteria and Fungi were maintained on nutrient agar slops (NA) and sabouraud agar (SA), respectively. When calculated, a loop full of baceria was grown on tryplic Saaybroth, while Fungi were subcultured on a yeast nitrogen base supplemented with glucose (YNBG). All media used were of dificagrade.

EXPERIMENTAL

All melting points are uncorrected; ir spectra (KBr) were recorded on a Perkin Elmer 2000 FT-ir spectrophotometer. Both ^1H and ^{13}C nmr spectra were recorded on a Brucker 400 MHz spectrometer with DMSO-d_6 or $CDCl_3$ as solvent using TMS as internal standard with chemical shifts reported in ppm (δ). Mass spectra were measured on GS/MS INCOL XL, Finingan MAT. Microanalyses were performed on a LECO CHNS 932 analyzer.

General Procedure for the Synthesis of **3a-c**.

A mixture of **1** (1.75 g, 0.01 mol) in DMF (20 ml) containing 2-3 drops of triethylamine was treated with each of arylaldehydes **2a-c** (0.01 mol). The reaction mixture was refluxed for 10-12 hours. The solid product, so formed, was collected by filtration and recrystallized from the proper solvent.

3-(1'-Benzotriazolyl)-4-phenyl-3-buten-2-one (**3a**).

This compound was recrystallized from ethanol to give yellow crystals in 69% yield, mp 88-89 °C; ir: ν_{max} 1697 cm^{-1} (CO), ^1H nmr (DMSO-d_6): δ_H: 2.68 (s, 3H, Me); 6.45 (s, 1H, =CH); 7.28-8.45 ppm (m, 9H, Ar-H); ^{13}C nmr (DMSO-d_6): 194.78 (CO), 163.27, 145.80, 143.11, 134.09, 132.29, 130.93, 129.94, 128.58, 125.38, 120.33, 118.81 and 111.28 (aromatic and vinylic carbons) and 26.63 ppm (Me).

Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.97; N, 15.95. Found: C, 72.79; H, 5.06; N, 15.79.

3-(1'-Benzotriazolyl)-4-(*p*-methoxyphenyl)-3-buten-2-one (**3b**).

This compound was recrystallized from ethanol to give yellow crystals in 81% yield, mp 123-125°C, ir: ν_{max}: 1675 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ_H: 2.72 (s, 3H, Me); 3.82 (s, 3H, OMe); 6.38 (s, 1H, =CH); 6.73-8.38 ppm (m, 8H, Ar-H); ^{13}C nmr (DMSO-d_6): δ_C 194.49 (CO), 162.77, 159.72, 145.91, 142.92, 134.07, 133.38, 129.94, 125.31, 124.34, 120.38, 115.81 and 111.27 (aromatic and vinylic carbons), 56.27 (OMe) and 26.63 ppm (Me).

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found : C, 69.79; H, 5.08; N, 14.47.

3-(1'-Benzotriazolyl)-4-(*p*-nitrophenyl)-3-buten-2-one (**3c**).

This compound was recrystallized from a mixture of ethanol/DMF (2:1) as brown crystals in 71% yield; mp 197-199 °C; ir: ν_{max} 1662 (CO); ^1H nmr (DMSO-d_6): δ_H 2.67 (s, 3H,

Me); 7.13-8.50 ppm (m, 9H, Ar-H & =CH); ms (EI): m/z= 308 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.24; H, 3.86; N, 18.12.

General Procedure for the Synthesis of **4a-c**.

Method A.

A mixture of compound **3a-c** (0.01 mol) and malononitrile (0.66 g, 0.01 mol) in absolute ethanol (20 ml) and a few drops of piperidine was refluxed for 4 hours, then poured onto cold water. The solid product, so formed, was collected by filtration and recrystallized from ethanol as pale yellow crystals.

Method B.

A mixture of compound **1** (1.75 g, 0.01 mol) and *p*-methoxybenzaldehyde (**2b**) (1.36 g, 0.1 mol) or *p*-nitrobenzaldehyde (**2c**) (1.51 g, 0.01 mol) in DMF (20 ml) and a few drops of piperidiene was refluxed for 8 hours. The mixture was then treated with malononitrile (0.66 g, 0.1 mol), refluxed for 5 hours, then allowed to cool, and poured onto ice-cold water. Each of the solid product so formed, was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1).

5-(1'-Benzotriazolyl)-6-methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (**4a**).

This compound was obtained as pale yellow crystals in 75% yield, mp 175-177 °C, ir: ν_{max}: 3411 (NH), 2193 (CN) and 1646 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ_H 2.20 (s, 3H, Me), 7.03-7.65 (m, 9H, Ar-H) and 10.20 ppm (br, 1H, NH, D_2O-exchangeable).

Anal. Calcd. for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.40. Found: C, 70.03; H, 4.08; N, 21.31.

5-(1'-Benzotriazolyl)-4-(*p*-methoxyphenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4b**).

This compound was obtained as deep brown crystals in 85% yield, mp 107-109 °C; ir: ν_{max}: 3336 (NH), 2186 (CN) and 1658 cm^{-1} (CO); ^1H nmr ($CDCl_3$): δ_H 2.31 (s, 3H, Me), 3.81 (s, 3H, OMe), 6.81-8.21 (m, 8H, Ar-H), 9.50 ppm (b, 1H, NH, D_2O-exchangeable); ^{13}C nmr (DMSO-d_6): δ_C 163.16 (C-2), 161.77 (C-6), 158.33, 146.05, 133.98, 131.41, 130.30, 129.52, 128.62, 128.15, 125.15, 120.14, 119.07, 115.10, 114.17 (aromatic carbons & CN), 111.50 (C-3), 55.51 (OMe) and 25.45 ppm (Me).

Anal. Calcd. For $C_{20}H_{15}N_5O_2$: C, 67.22, H, 4.23, N, 19.59. Found: C, 67.36, H, 4.18; N, 19.46.

5-(1'-Benzotriazolyl)-6-methyl-4-(p-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4c**).

This compound was obtained as deep brown crystals in 92% yield, mp 160-162 °C; ir: ν_{max}: 3345 (NH), 2203 (CN) and 1631 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ_H 2.21 (s, 3H, Me), 7.18-8.26 (m, 8H, Ar-H), 10.60 ppm (b, 1H, NH); ^{13}C nmr (DMSO-d_6): δ_C 166.77 (C-2); 165.12 (C-6), 154.00, 149.72, 145.94, 143.70, 136.12, 133.90, 131.41, 128.76, 127.53, 125.10, 124.73, 120.18 (aromatic carbons), 118.21 (CN), 115.58 (C-3) and 21.83 ppm (Me).

Anal. Calcd. for $C_{19}H_{12}N_6O_3$: C, 61.29; H, 3.24; N, 22.56.Found: C, 61.39; H, 3.24; N, 22.65.

5-(1'-Benzotriazolyl)-4-methyl-6-(*p*-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**5**).

A mixture of compound **6** (2.41 g, 0.01 mol) and *p*-nitrobenzaldehyde **2c** (1.51 g, 0.01 mol) in absolute ethanol (20 ml) was refluxed for 5 hours, then allowed to cool, poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1) as deep brown crystals in 71 % yield, mp 110-112 °C. ir: ν_{max}: 3345 (NH), 2203 (CN) and 1631 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ_H 2.31 (s, 3H, Me); 7.18 -8.26, (m, 8H, Ar-H); 10.50 ppm (b, H, NH).

Anal. Calcd. $C_{19}H_{12}N_6O_3$: C, 61.29; H, 3.24; N, 22.56. Found: C, 61.46; H, 3.40; N, 22.79.

4-(1'-Benzotriazolyl)-2-cyano-3-methyl-2-butenamide (**6**).

A mixture of **1** (1.75 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mmol) in ethanol (20 ml) and few drops of triethylamine. The reaction mixture was refluxed for 2 hours, then poured onto ice-cold water and neutralized with HCl (10%). The solid product so formed was collected by filtration and recrystallized from ethanol to give yellow crystal in 89% yield; mp 130-132 °C; ir: ν_{max}: 3405-3339 (NH_2), 2190 (CN) and 1666 cm^{-1} (CO); ^1H nmr (DMSO-d_6); δ_H 2.30 (s, 3H, Me), 6.02 (s, 2H, CH_2), 7.27-8.10 (m, 4H, Ar-H) and 8.60 ppm (b, 2H, NH_2).

Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.82; H, 4.70; N, 29.10.

General Procedure for the Synthesis of **7a-b**.

A solution of each **3a**-**b** (0.01 mol) in absolute ethanol (30 ml) was treated with malononitrile (0.66 g, 0.01 mol) and sodium ethoxide (prepared from 0.60 g of sodium metal and 60 ml of ethanol). The mixture was refluxed for 5 hours, then poured onto ice cold water and neutralized with hydrochloric acid (10%). Each of the solid product so formed was collected by filtration and recrystallized from ethanol.

5-(1'-Benzotriazolyl)-2-ethoxy-6-methyl-4-phenylpyridine-3-carbonitrile (**7a**).

This compound was obtained as brown crystals in 76% yield; mp 135-137°C; ir: ν_{max}: 2203 cm^{-1} (CN); ^1H nmr (DMSO-d_6): δ 1.06 (t, 3H, J=7Hz, Me), 2.22 (s, 3H, Me), 3.45 (q, 2H, J=7Hz, OCH_2) and 7.16-8.32 ppm (m, 9H, Ar-H).

Anal. Calcd. $C_{21}H_{17}N_5O$: C, 70.96; H, 4.82; N, 19.71. Found: C, 70.79; H, 4.97; N, 19.18.

5-(1'-Benzotriazolyl)-2-ethoxy-4-(*p*-methoxyphenyl)-6-methylpyridine-3-carbonitrile (**7b**).

This compound was obtained as pale brown crystals in 78% yield; mp 174-176 °C; ir: ν_{max}: 2216 cm^{-1} (CN), ^1H nmr ($CDCl_3$): δ_H 1.33 (t, 3H, J=7Hz, Me), 2.30 (s, 3H, Me), 3.86 (s, 3H, OMe), 4.19 (q, 2H, J=7Hz, OCH_2), 6.40-8.35 (m, 8H, Ar-H); ^{13}C nmr (DMSO-d_6): δ_C 168.36 (C-2), 166.32 (C-6), 161.58, 159.24, 134.41, 132.16, 131.09, 130.64, 130.00, 129.72, 129.12, 128.65, 119.97, 117.45, 114.87 and 111.31 (aromatic carbons and CN), 55.86 and 52.92 (OCH_2 & OMe), 25.48 (Me) and 16.08 ppm (Me).

Anal. Calcd. for $C_{22}H_{19}N_5O_2$: C, 68.56, H, 4.97, N, 18.17. Found: C, 68.38, H, 4.86, N, 18.36.

5-(1'-Benzotriazolyl)-2-ethoxy-6-(*p*-methoxyphenyl)-4-methylpyridine-3-carbonitrile hydrochloride (**8**).

A mixture of compound **6** was treated with *p*-methoxybenzaldehyde (1.54 g, 0.01 mol) in sodium ethoxide solution (30 ml of ethanol in 0.6 g sodium). The reaction mixture was refluxed for 3 hours, left to cool then acidified with 10% of HCl. The solid product, so formed, was collected by filtration and recrystallized from a

mixture of EtOH/DMF (2:1) to give pale yellow crystals in 92% yield; mp 140-142 °C ir: ν_{max}: 2216 cm^{-1} (CN). ^1H nmr (DMSO-d_6): δ_H 1.12 (t, 3H, J=7H), 2.37 (s, 3H, Me); 3.81 (s, 3H, OMe); 4.16 (q, 2H, J=7Hz, OCH_2); 6.72-7.88 (m, 8H, Ar-H).

Anal. Calcd. for $C_{22}H_{20}N_5O_2Cl$: C, 62.63; H, 4.77; N, 16.60. Found: C, 62.50; H, 5.11; N, 16.32.

1-[(3'-Methyl-(1*H*)-5'-(*p*-methoxyphenyl)pyrazol-4'-yl)]benzotriazole (**9**).

A solution of **3b** (2.93 g, 0.01 mol) in ethanol (20 ml) was treated with hydrazine hydrate (0.5 g, 0.01 mol). The reaction mixture was refluxed for 2 hours then allowed to cool. The solid product, so formed, was collected by filtration and recrystallized from ethanol to give yellow crystals in 73% yield; mp 160-162 °C; ir: ν_{max} 3402 cm^{-1} (NH); ^1H nmr (DMSO-d_6): δ_H 2.17 (s, 3H, Me), 3.42 (s, 3H, OMe), 6.20-8.20 (m, 8H, Ar-H) and 10.50 ppm (b, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.93. Found: C, 66.97; H, 5.02; N, 22.83.

5-(1'-Benzotriazolyl)-3-benzoyl-4-(*p*-methoxyphenyl)-6-methyl-2-oxo-1,2-dihydropyridine (**10**).

A solution of compound **1** (1.75 g, 0.01 mol) in DMF (20 ml) was treated with *p*-methoxybenzaldehyde (**2b**) (1.21 g, 0.01 mol) and a few drops of piperidine. The reaction mixture was refluxed for 8 hours then treated with benzoylacetonitrile (1.45 g, 0.01 mol) and refluxed for another 5 hours then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1) to give yellow crystals in 72% yield, mp 118-120 °C; ir: ν_{max}: 3352 (NH), 1692 (CO) and 1650 cm^{-1} (CO); ^1H nmr (DMSO-d_6); δ_H 2.20 (s, 3H, Me), 3.82 (s, 3H, OMe), 6.88-7.95 (m, 13H, Ar-H) and 8.25 ppm (b, 1H, NH).

Anal. Calcd. For $C_{26}H_{20}N_4O_3$: C, 71.55; H, 4.62; N, 12.82. Found: C, 71.87; H, 4.32; N, 13.09.

8-Amino-4-(1'-Benzotriazolyl)-1-ethoxy-3-(*p*-methoxyphenyl)-6-phenyl-6,7-dihydroisoquinoline-7,7-dicarbonitrile hydrochloride (**11**).

A solution of **8** (4.21 g, 0.01 mol) in 20 ml of ethanol and few drops of piperidine was treated with benzylidenemalononitrile (1.54 g, 0.01 mol). The reaction mixture was refluxed for 5 hours and then poured onto cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of DMF/EtOH (2:1) as brown crystals in 83% yield; mp 167-169 °C; ir: ν_{max}: 3339-3195 (NH_2); 2223 and 2189 cm^{-1} (2CN); ^1H nmr (DMSO-d_6): δ_H 1.34 (t, 3H, J-7Hz, Me), 2.55 (m, 1H, H-6), 3.75 (s, 3H, OMe), 4.42 (q, 2H, J=7Hz, OCH_2), 6.60-7.86 (m, 14H, Ar-H & H-5), 7.97 ppm (bs, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ_C 165.68 (C-1), 162.61, 161.63 (C_4 & C_8), 155.22, 146.11, 145.71, 144.65, 143.86, 135.41, 131.52, 130.56, 129.68, 129.41, 129.38, 129.28, 129.17, 128.78, 120.11, 119.82, 115.49, 114.68, 111.74 and 107.30 (aromatic carbons 2CN) 56.21 and 56.83 (OCH_2 & OCH_3), 26.52 (C-6), 21.87 (Me) and 18.90 ppm (C-7).

Anal. Calcd. For $C_{32}H_{26}N_7O_2Cl$: C, 66.72, H, 4.54, N, 17.02. Found: C, 66.80, H, 4.29, N, 17.17.

3-Amino-7-(1'-Benzotriazolyl)-4-ethoxy-6-(*p*-methoxyphenyl)-thieno[3,4-*c*]pyridine (**12**).

A solution of **8** (4.21 g, 0.01 mol) in 20 ml of EtOH/DMF (2:1) was treated with element al sulfur (0.32 g, 0.01 mol) and piperidine (0.2 ml). The mixture was refluxed for 4 hours then poured onto water. The solid product, so formed, was collected by filtration and recrystallization from a mixture of EtOH/DMF (2:1) to give green crystals in 76% yield, mp 155-157 °C; ir: ν_{max}: 3448, 3383 cm^{-1} (b, NH_2); ^1H nmr (DMSO-d_6): δ_H 1.21 (t, 3H, J=7Hz, Me); 3.81 (s, 3H, OMe); 4.14 (q, 2H, J=7Hz, OCH_2), 6.64-7.86 (m, 9H, Ar-H & H-1) and 8.54 (bs, 2H, NH_2, D_2O-exchangeable).

Anal. Calcd. for $C_{22}H_{19}N_5O_2S$: C, 63.30; H, 4.59; N, 16.78. Found: C, 63.29; H, 4.71; N, 16.72.

Dimethyl-4-amino-9-(1'-Benzotriazolyl)-6-ethoxy-8-(*p*-methoxyphenyl)thiepino[3,4-*c*]pyridine-2,3-dicarboxylate (**15**).

A mixture of **12** (4.17g, 0.01 mol) and DMAD (1.23 g, 0.01 mol) in dioxane (20 ml) and acetic acid (2 ml) was refluxed for 8 hours then poured onto ice cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of DMF/EtOH (2:1) as green crystals in 74% yield, mp 170-172 °C ; ir: ν_{max} 3410, 3380 (NH_2) and 1735 cm^{-1} (2CO); ^1H nmr (DMSO-d_6): δ_H 1.17 (t, 3H, J=7H, Me), 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.05 (q, 2H, J=7Hz, OCH_2), 6.99 (s, 1H, H-1), 7.05-8.00 (m, 8H, Ar-H) and 8.02 ppm (bs, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ_C 166.66 (CO), 164.85 (CO), 161.61 (C-6), 155.28 (C-8), 148.03, 146.09, 145.57, 144.63, 142.13, 135.39, 130.75, 129.89, 129.25, 128.88, 128.22, 125.38, 123.48,120.46, 117.46, 115.57, 114.68 (aromatic carbons), 67.38 (OCH_2), 56.30 (3OMe) and 19.45 ppm (Me).

Anal. Calcd. for $C_{28}H_{25}N_5O_6S$: C, 60.10; H, 4.50; N, 12.52. Found: C, 60.20; H, 4.41; N, 12.81.

3-[3'-Amino-7'-(1"-benzotriazolyl)-4'-ethoxy-6'-(*p*-methoxyphenyl)thieno-[3,4-*c*]pyridin-1-yl]-1-(2-thienyl)-2-propen-1-one (**17**).

To a solution of **12** (4.17 g, 0.01 mol) in a mixture of dioxane (20 ml) and acetic acid (2 ml) was treated with 3-(*N,N*-dimethylamino)-1-(2'-thienyl)-2-propen-1-one (**16**) (1.81 g, 0.01 mol). The reaction mixture was refluxed for 8 hours and poured onto ice cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of DMF/EtOH (2:1) to give green crystals in 73% yield, mp 158-160 °C, ir: ν_{max}: 3447 and 3342 (NH_2) and 1654 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ_H 1.21 (t, 3H, J=7Hz, Me), 3.81 (s, 3H, OMe), 4.18 (q, 2H, J=7Hz, OCH_2), 5.85 (d, 1H, J=15 Hz, vinylic-H) 6.39 (d, 1H, J=15Hz, vinylic-H), 6.38-8.30 (m, 11H, Ar-H) and 8.42 ppm (b, 2H, NH_2); ^{13}C (DMSO-d_6): δ_C 188.99 (CO ketone), 165.66, 164.84, 161.27, 155.28, 148.04, 145.70, 144.63, 143.83, 142.12, 135.39, 130.75, 129.89, 129.53, 128.88, 128.32, 125.46, 123.47, 120.46, 115.70, 115.10, 114.68, 111.23, 110.85 (aromatic & vinylic carbons), 67.37 (OCH_2), 56.24 (OMe) and 19.46 ppm (Me).

Anal. Calcd. for $C_{29}H_{23}N_5O_3S_2$: C, 62.92, H, 4.19, N, 12.65. Found: C, 63.06, H, 4.37, N, 12.40.

2-(1'-Benzotriazolyl)-1,5-bis(*p*-nitrophenyl)-1,4-pentadien-3-one (**18**).

A mixture of **1** (1.75 g, 0.01 mol) in DMF (20 ml) containing 2-3 drops of triethylamine was treated with *p*-nitrobenzaldehyde (**2c**) (3.02 g, 0.02 mol). The reaction mixture was refluxed for 12-14 hours then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from a

mixture of EtOH/DMF (2:1) as brown crystals in 81% yield, mp. 166-168 °C, ir: ν_{max}: 1662 (CO); ^{1}H nmr (DMSO-d_6): δ_H 6.84 (s, 1H, =CH), 7.01-8.43 (m, 14H, Ar-H & vinylic–H).

Anal. Calcd. for $C_{23}H_{15}N_5O_5$: C, 62.58; H, 3.42; N, 15.87. Found: C, 62.58; H, 3.53; N, 15.62.

General Procedure for the Synthesis of **19-20**.

A solution of **18** (4.41 g, 0.01 mol) in 20 ml of ethanol was treated with hydrazine hydrated (0.5 g, 0.01 mol) or hydroxylamine hydrochloride (0.69 g, 0.01 mol). The reaction mixture was refluxed for 1 hour and left cool at room temperature. Each of the solid product so formed was collected by filtration and recrystllized from ethanol.

1-{2'-(*p*-Nitrophenyl)-1'-[5"-(*p*-nitrophenyl)-1"*H*-pyrazol-3"-yl]-vinyl}benzotriazole (**19**).

This compound was obtained as yellow crystals in 61% yield; mp 210-212 °C; ir: ν_{max} (NH); ^{1}H nmr (DMSO-d_6): δ_H 6.30 (s, 1H, pyrazol-H), 6.72 (s, 1H, =CH), 7.22-8.22 (m, 12H, Ar-H) and 8.80 ppm (b, 1H, D_2O-exchangeable NH).

Anal. Calcd. for $C_{23}H_{15}N_7O_4$: C, 60.87; H, 3.33; N, 21.62. Found: C, 60.76; H, 3.13; N. 21.82.

1-{2'-(*p*-Nitrophenyl)-1'-[5"-(*p*-nitrophenyl)isoxazol-3"-yl]-vinyl}benzotriazole (**20**).

This compound was obtained as a yellow brown solid in 79% yield, mp 190-192 °C; ^{1}H nmr (DMSO-d_6): δ_H 6.43 (s, 1H, H-4), 6.82 (s, 1H, =CH), 7.01-8.31 (m, 12H, Ar-H).

Anal. Calcd. for $C_{23}H_{14}N_6O_5$: C, 60.79; H, 3.10; N, 18.49. Found: C, 61.03; H, 3.32; N, 18.67.

General Procedure for the Synthesis of **21-22**.

To suspension of compound **18** (4.41 g, 0.01 mol) in 20 ml of ethanol was treated with malononitrile (0.66 g, 0.01 mol) or benzoylacetonitrile (1.45g, 0.01 mol) and few drops of piperidine. The reaction mixture was refluxed for 6 hours. The solvent was evaporated under reduced pressure. Each of the solid product, so formed, was collected by filtration and recrystallized from proper solvent.

6-[1'-(1-Benzotriazolyl)-2'-(*p*-nitrophenyl)vinyl]-4(*p*-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile hydrochloride (**21**).

This compound was recrystallized from ethanol as brown crystals in 76% yield; mp 180-182 °C; ir: ν_{max} 3379 (b, NH), 2192 (CN) and 1657 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ_H 6.68 (s, 1H, =CH), 7.03-8.30 (m, 13H, Ar-H & H-5) and 10.80 ppm (b,1H, NH).

Anal. Calcd. for $C_{26}H_{16}N_7O_5Cl$: C, 57.62; H, 2.97; N, 18.09. Found: C, 57.69; H, 3.14; N, 18.20.

6-[1'-(1-Benzotriazolyl)-2'(*p*-nitrophenyl)vinyl]-3-benzoyl-4-(*p*-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**22**).

This compound was recrystallized from a mixture of EtOH/DMF (2:1) as reddish brown crystals in 73% yield; mp 163-165 °C; ir: ν_{max} 3367 (NH), 1697 and 1632 cm^{-1} (2CO); ^{1}H nmr (DMSO-d_6): δ_H 7.01 (s, 1H, =CH), 7.03 (s, 1H, H-5), 7.29-7.98 (m, 17H, Ar-H), 8.05 ppm (br, 1H, NH, D_2O exchangeable).

Anal. Calcd for $C_{32}H_{20}N_6O_6$: C, 65.75; H, 3.45; N, 14.38. Found: C, 65.38; H, 3.37; N, 14.37.

6-[1'-(1-Benzotriazolyl)-2'-(*p*-nitrophenyl)vinyl]-2-ethoxy-4-(*p*-nitrophenyl)pyridine-3-carbonitrile hydrochloride (**23**).

A mixture of **18** (4.41 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in absolute ethanol (50 ml) was treated with sodium ethoxide (prepared from 0.6 g sodium metal and 60 ml of ethanol). The reaction mixture was refluxed for 3 hours, then poured onto cold water and neutralized with hydrochloric acid (10%). The solid product was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1) as brown crystals 68% yield, mp 250-252 °C ir: ν_{max} 2191 cm^{-1} (CN); ^{1}H nmr (DMSO-d_6): δ_H 1.23 (t, 3H, J=7Hz, Me), 4.36 (q, 2H, J=7Hz, OCH_2), 6.94 (s, 1H, =CH), 7.22-8.13 ppm (m, 13H, Ar-H & H-5).

Anal. Calcd. for $C_{28}H_{20}N_7O_5Cl$: C, 59.00; H, 3.53; N, 17.20. Found: C, 59.12; H, 3.43; N, 17.01.

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 (0.01 mol) was poured aseptically in a well of 6 mm diameter made by a Cork borer in the nutrient agar medium for bacterial test and in Sabourand agar for fungal test. After placing the same volume in wells of all tested microorganisms nutrient agar plates were incubated at 37 °C for 24 h and sabourand dextrose agar plates were incubated at 25 °C for 48 hours The activities were expressed as inhibition zones (mm, diameter, as clear areas) as antibacterial and antifungal effect. The least concentration, which showed inhibitory effect on any specific micoorganism, was considered as the minimum inhibitory concentration (MIC) that was determined using *streptomycin* (50 μg/ml) as the references.

Acknowledgement.

This work was financed by University of Kuwait, Research Grant SC 08/00. We are grateful to the Faculty of Science, Chemistry Department, SAF facility for the analytical and spectral measurement (Project G01/01 & G 03/01). We are also grateful to Dr. I.H. Abbas for the biological activity tests.

REFERENCES AND NOTES

[1] F. Herencia, M. Ferrandiz, A. Ubeda, J. Dominguez, J. Charris, G. Lobo and M. *Alcarz, Biog & Medicinal Chem. Letters*, **8**, 1169 (1998).

[2] S. Ducki, R. Forrest, J.A. Hadfield, A. Kendall, N. Lawrence, A. McGown and D. Rennison, *Biorg & Medicianal Chem. Letters*, **8**, 1051 (1998).

[3] A. Sengupta, M. Bajaj and V. Chand, *J. Indian. Chem. Soc.*, **55**, 992 (1978).

[4] S. El-Khawass and N. Habib, *J. Heterocyclic Chem.* **26**, 177 (1989)

[5] L. Bannett and H. Baker, *J. Org. Chem.*, **22**, 707 (1957).

[6] S. Rao and A. Mitra. *Indian. J. Chem.*, **15B**, 1060 (1977).

[7] S. Srivatava and T. Rawat, *Indian J. Chem.*, **38B**, 623 (1999).

[8] F. Al-Omran, *J. Heterocyclic Chem.*, **37**, 1219 (2000).

[9] F. Al-Omran, N. Al-Awadi, O. Yousef and M. Elnagdi., *J. Heterocyclic Chem.*, **37**, 167 (2000).

[10] F. Al-Omran, O. Yousef and Adel Abou El-Khair, *J. Heterocyclic Chem.*, **37**, 1617 (2000).

[11] F. Al-Omran, Rafat M. Mohareb and Adel Abou El-Khair, *J. Heterocyclic Chem.*, **39**, 877 (2002).

[12] F. Al-Omran, N. Al-Awadi, *J. Chem. Res.(S)*, 392 (1995); *J. Chem. Res.(M)*, 2201, (1995).

[13] F. Al-Omran, N. Al-Awadi, and M. Edun, *J. Chem. Res.(S)*, 168 (1994); *J. Chem. Res.(M)*, 1026 (1994).

[14] H. Al-Awadhi, F. Al-Omran, M. H. Elnagdi, L. Infantes, C. Foces-Foces, N. Jagerovic and J. Elguero, *Tetrahedron*, **46**, 12745 (1995).

[15] F. Al-Omran, M. Abdel Khalik, H. Al-Awadhi and M. Elnagdi, *Tetrahedron*, **52**, 11915 (1996).

[16] F. Al-Omran, *Sulfur Letters*, **23(6)**, 275 (2000).

[17] F. Al-Omran, N. Al-Awadi, A. A. Elassar and A. A. El-Khair, *J. Chem. Res.(S),* 20 (2000); *J. Chem. Res.(M),* 237 (2000).

[18] N. Nyiondi-Bonguen, E.S. Fondjo, Z. T. Fomum, D. Dopp, *J. Chem. Soc. Perkin Trans 1*, 2191 (1994).

[19] A. Al-Etaibi, N. Al-Awadi, F. Al-Omran, M. Abdel-Khalek and M. Elnagdi, *J. Chem. Res.(S),* 4 (1999); *J. Chem. Res. (M),* 151 (1999).