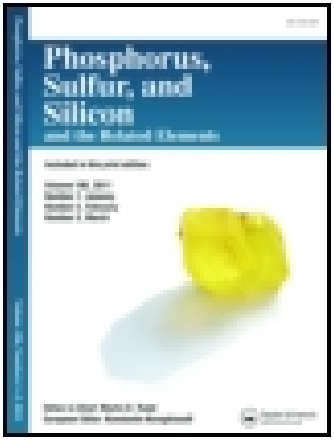

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SYNTHETIC POTENTIALITIES OF THIOPHENE SYSTEMS IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF THIENO[2,3-b]PYRIDINE DERIVATIVES

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SYNTHETIC POTENTIALITIES OF THIOPHENE SYSTEMS IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF THIENO[2,3-*b*]PYRIDINE DERIVATIVES

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The reactivity of thiophene derivatives **1,2** and **3** towards active methylene reagents, aryledenemalononitriles were studied to afford several new thieno[2,3-b]pyridine derivatives. The biological activities of the synthesized products showed interesting results.

Keywords: Thiophenes; active methylenes; aryldenemalononitriles

INTRODUCTION

Thiophene systems are progressively important derivatives as biologically and pharmaceutically active constituents, and are considered as the fundamental key structure units in sulfur containing heterocycles.[1–4]

RESULTS AND DISCUSSION

Recently, our research group has studied the reactivity of thiophene derivatives as precursors for the synthesis of a vast variety of fused thiophene systems of potential biological activity.[5–9]

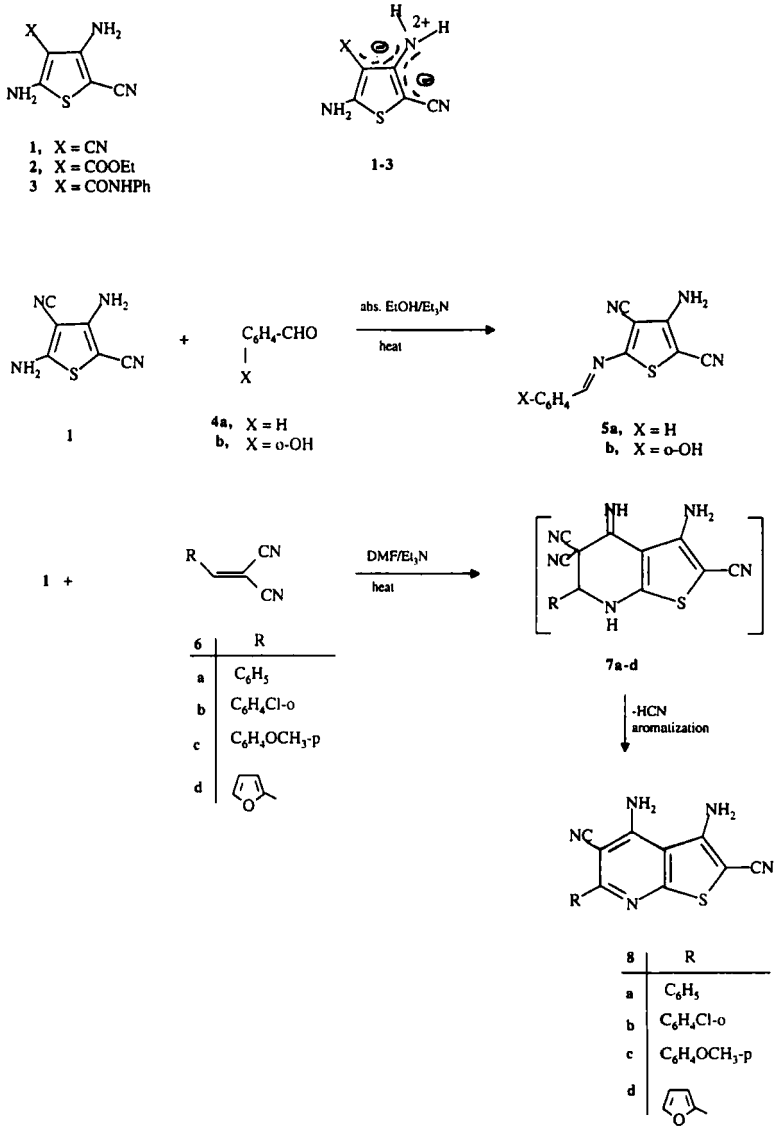
* Correspondence Author.

As a continuation to this study, we oriented our research program towards investigating new routes for the synthesis of thienopyridine derivatives with expected biological activity. The key precursors in such synthetic routes were compounds **1**[10,11], **2** and **3** (Exp. Section).

It is noteworthy that the presence of two electron-withdrawing moieties, flanking C-4 amino group in compounds **1–3**, decrease its reactivity with respect to its C-2 counterpart. This may be explained by the hindered delocalization effect on the lone pair of electrons localized on C-4 NH_2 which leads to its existence in the anion form.

Based on the foresaid assumption, the reactivity of compounds **1–3** towards different reagents was studied. It was found that the reaction of compound **1** with aromatic aldehydes; namely benzaldehyde (**4a**) and salicylaldehyde (**4b**), afforded the benzylidene condensates **5a,b**, respectively. Structures **5a, b** were established based on analytical and spectral data. IR spectra revealed the presence of stretching modes at 3560–3344 cm^{-1} corresponding to NH_2 group in case of **5a** or OH and NH_2 moieties in case of **5b**. Two absorption bands at 2220 and 2215 cm^{-1} attributed to two CN groups were also revealed in the IR spectra of **5a,b**. The ^1H NMR spectrum of **5b** displayed a singlet at δ 4.79 (2H) ppm (D_2O-exchange-able) corresponding to NH_2 group, a multiplet at δ 7.01–7.32 (5H) ppm attributed to aromatic protons and ylidene CH, as well as a singlet at δ 9.98 (1H) ppm due to OH proton.

The reactivity of compound **1** towards β-addition was studied through the treatment of **1** with ethylenedicarbonitrile reagents. Thus, the treatment of **1** with **6a-d** afforded the corresponding thieno[2,3-*b*]pyridine derivatives **8a-d**, respectively. A logic mechanism for the latter reactions was based on the intermediate formation of the 4-imino-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridine derivatives **7a-d**. The latter, being highly unstable, were readily converted into the stable isolable 4-amino-thieno[2,3-*b*]pyridine derivatives **8a-d** *via* dehydrocyanation followed by prototropic shift and aromatization. Thieno[2,3-*b*]pyridine structure assigned for the reaction products **8a-d** was based on their molecular formulae and on their spectral data. Thus, IR spectra showed the presence of two NH_2 stretching modes at 3450–3200 cm^{-1} and two CN stretchings at 2220–2210 cm^{-1}, (IR), as well as two D_2O-exchangeable proton singlets at δ 2.70–4.20 due to two NH_2 protons (^1H NMR) confirms the assigned thieno[2,3-*b*]pyridine structure **8a-d**. The ^1H NMR spectra of **8a-c** revealed aromatic proton nultiplets at δ 7.15–7.90 ppm, while **8d** revealed signals of furan protons at



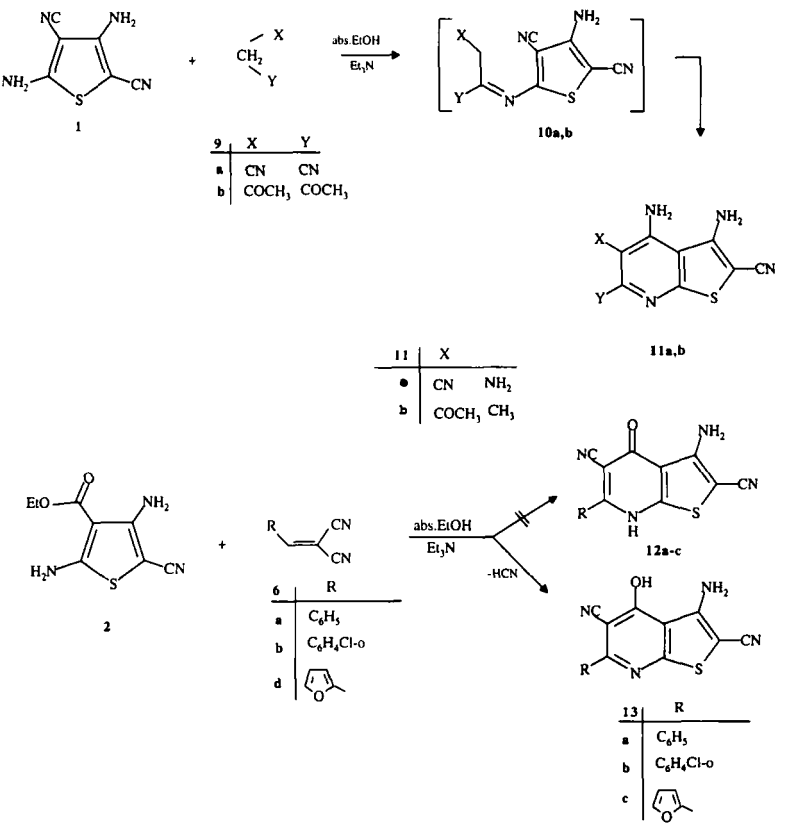
SCHEME 1

δ 6.17–7.60 (3H) ppm. A characteristic OCH_3 proton singlet at δ 3.75 (3H) ppm was also displayed in the ^1H NMR spectrum of **8c**.

On the other hand, the reaction of compound **1** with active methylene reagents was also investigated. Thus, the treatment of equimolar amounts of **1** with each of malononitrile (**9a**) or acetylacetone (**9b**) afforded the corresponding thieno[2,3-*b*]pyridine derivatives **10a,b**, respectively, in reasonable yields. The reaction was assumed to proceed *via* the intermediacy of the expected acyclic intermediates **10a,b** which readily underwent intramolecular ionic cyclization through the active methylene moiety. Assignment of structures **11a,b** was based on their consistency with the data obtained from elemental analyses and spectral data. The IR spectrum of **11a** showed strong NH_2 stretching modes at 3495–3200 cm^{-1} corresponding to three NH_2 groups as well as two typical CN stretching lines at 2225 and 2220 cm^{-1}. Also, its ^1H NMR spectrum (DMSO-d6) exhibited three D20-exchangeable singlets at δ 2.76 (2H), δ 3.12 (2H) and δ 4.30 (2H) ppm, corresponding to three NH_2 groups, respectively. Compound **11b** revealed, in its IR spectrum, stretching bands at 3400–3250 cm^{-1} attributed to two NH_2 functions, a stretching mode at 2215 cm^{-1} due to CN group and a sharp characteristic C=O stretching at 1710 cm^{-1}. The ^1H NMR spectrum of **11b** exhibited two CH_3 singlets at δ 2.58 and δ 2.95 (3H each) ppm corresponding to methyl and carboxomethyl protons as well as two D_2O-exchangeable singlets at δ 3.28 and δ 3.95 (2H each) ppm due to two NH_2 groups.

To assess the scope and generality of this methodology aimed at the facile synthesis of thieno[2,3-*b*]pyridine derivatives, the behavior of C-2 NH_2 function in compound **2** towards different reagents was examined. Nucleophilic attack by C-2 NH_2 group on ethylenedicarbonitrile reagents **6a,b,d** afforded the corresponding 4-hydroxythieno[2,3-*b*]pyridine compounds **13a-c** not the thieno[2,3-*b*]pyridin-4-one derivatives **12a-c**. The identity of structures **13a-c** was established on the basis of their elemental and spectral data. The IR spectra of **13a-c** revealed the presence of both OH and NH_2 stretching modes about 3560–3320 cm^{-1} as well as two CN stretchings about 2225–2210 cm^{-1}. The ^1H NMR spectrum of **13c**, as an example, showed two types of D_2O-exchangeable protons at δ (ppm) 4.40 (s, 2H, NH_2) and 9.20 (s, 1H, OH) as well as three proton signals of furan moiety at δ 6.20–7.72 (3H) ppm.

At the other extreme, on subjecting compound **2** to a reaction route similar to that adopted for the reaction of **1** with active methylene reagents; namely malononitrile (**9a**), acetylacetone (**9b**), ethyl cyanoacetate (**9c**) or ethyl acetoacetate (**9d**), the corresponding thieno[2,3-*b*]pyridine deriva-

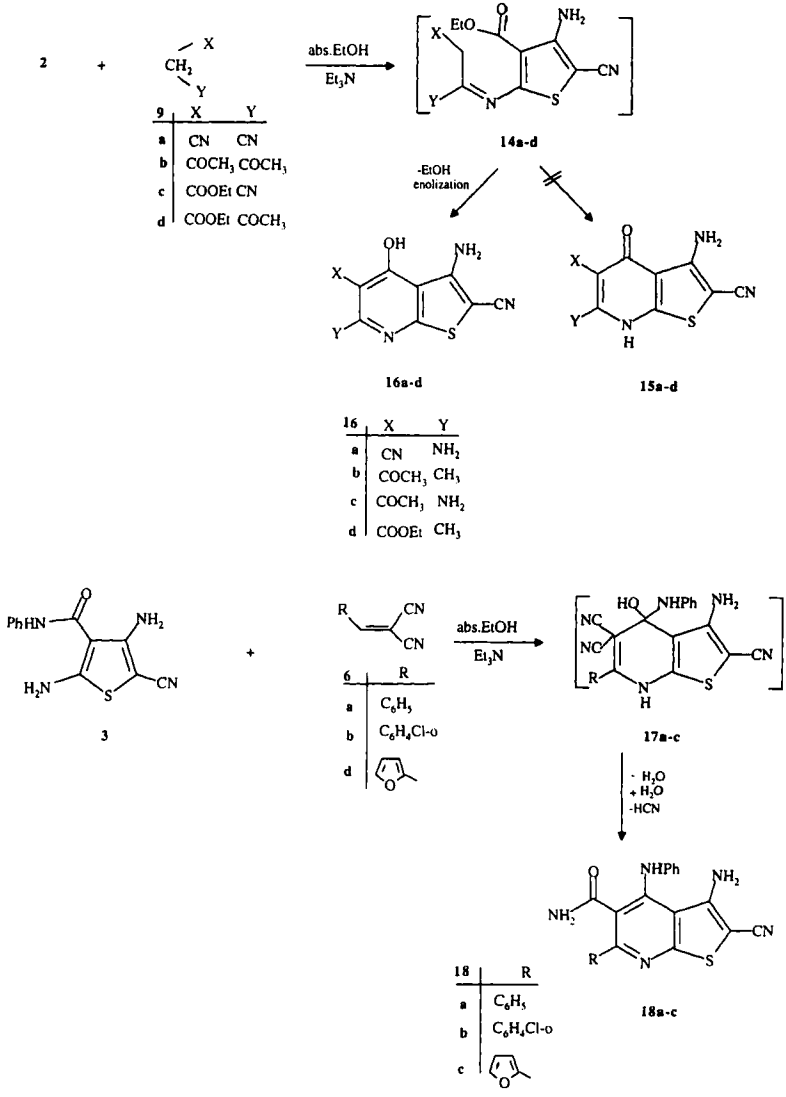


SCHEME 2

tives **16a-d**, respectively, were obtained not the thieno[2,3-*b*]pyridin-4-one derivatives **15a-d**. The nature of the reaction products depended on the selectivity of cyclization of the formed acyclic intermediates **14a-d**. Thus, in case of **9a** and **9c** the formed intermediates **14a** and **14c**, respectively, resulted *via* nucleophilic attack by C-2 NH_2 function in **2** on the carbonitrile moiety in the active methylene reagents. On the other hand, the acyclic intermediates **14b** and **14d** resulted *via* C-2 NH_2 attack on the carboxomethyl moiety in **9b** and **9d**, respectively. The resulting non-isolable intermediates **14a-d** underwent intramolecular ionic cyclization through the active methylene moiety *via* elimination of ethanol followed by subsequent enolization to give the final products **16a-d**. The assigned

structures of **16a-d** as the reaction products not the thieno[2,3-b]pyridin-4-one derivatives **15a-d** were based on the data exhibited by their microanalyses, IR and ^{1}H NMR spectra. IR spectra showed in addition to the characteristic OH and NH_2 absorption modes of **16a-d**, two CN stretchings at 2215–2210 cm^{-1} in case of **16a** as well as the absence of any C=O stretching which might be expected to appear if structure **15a** is considered. Moreover, the presence of one CN and one C=O stretchings bands at 2220–2210 cm^{-1} and 1715–1700 cm^{-1}, respectively, in case of **16b-d.** The ^{1}H NMR spectrum of **16a** revealed two D_2O-exchangeable singlets at δ 2.50 and δ 3.20 (2H each) ppm due to two NH_2 functions as well as one OH proton singlet (D_2O-exchangeable) at δ 11.20 ppm. Compound **16c** showed, in its ^{1}H NMR spectrum, a triplet at δ 1.39 (3H) ppm and a quartet at δ 4.23 (2H) ppm, representing ethyl ester moiety. Two NH_2 singlets (D_2O-exchangeable) at δ 2.90 and δ 3.20 (2H each) ppm as well as one D_2O-exchangeable OH proton singlet at δ 10.85 ppm were also revealed in the ^{1}H NMR spectrum of **16c**. Compound **16b** exhibited, in its ^{1}H NMR spectrum, two singlets at δ 2.45 and δ 2.64 (3H each) ppm due to two CH_3 protons and two D_2O-exchangeable singlets at δ 3.95 (2H) and δ 11.30 (1H) ppm corresponding to the NH_2 and OH groups, respectively.

As a continuation to our study aimed to synthesize thienopyridine derivatives of expected biological activity, the thiophene derivative **3** was subjected to reagents similar to those adopted in case of compounds **1** and **2**. Thus, the treatment of **3** with ethylenedicarbonitrile derivatives **6a,b,d** afforded the corresponding thieno[2,3-*b*]pyridine derivatives **18a-c**, respectively. The mechanismic pathway assumed to be followed was an initial β-addition by C-2 NH_2 function in compound **3** to the conjugate double bond in the ethylenedicarbonitrile derivatives **6a, b, d** followed by intramolecularly cyclized into the cyclic intermediates **17a-c** which, in turn, suffered water elimination followed by subsequent hydrolysis on one of the carbonitrile functions of the pyridine moiety to give the final isolable products **18a-c** *via* dehydrocyanation followed by prototropic shift aromatization. Structures **18a-c** were explained in terms of their molecular formulae and their spectral data. The IR spectrum of **18a-c** were analyzed as two NH_2 and one NH modes about 3440–3190 cm^{-1} and one CN stretching line about 2225–2215 cm^{-1}. The absence of a second CN stretching expected about 2220–2210 cm^{-1} and the presence of a C=O stretching line about 1668–1660 cm^{-1} confirms the assignment of carbonitrile hydrolysis of the pyridine moiety to an amido function. The ^{1}H NMR



SCHEME 3

spectra of **18b,c** showed two broad D_2O-exchangeable NH_2 proton singlets at δ 2.90–4.20 (2H each) ppm as well as one D_2O-exchangeable NH proton singlet at δ 8.61–9.30 (1H) ppm. Two aromatic proton multiplets at

δ 7.31 and δ 8.20 ppm were exhibited in case of **18b** while compound **18c** showed a multiplet at δ 6.10–7.80 (3H) ppm representing furan protons.

Subjecting the thiophene derivative **3** to react with active methylene reagents **9a-d**, the corresponding thieno[2,3-*b*]pyridine derivatives **20a-d**, respectively, were obtained. The reaction of 3 with active methylene reagents afforded **20a-d** through intramolecular cyclization of the formed acyclic intermediates **19a-d**. A hydrolysis step took place in case of **20a** during the cyclization sequence which was a subsequent step following water elimination. Confirmation of structures **20a-d** was based on their analytical and spectral data. The IR spectrum of **20a** revealed a broad absorption band in the range of 3500–3201 cm^{-1} due to three NH_2 and one NH functions, a stretching band at 2225 cm^{-1} corresponding to CN function as well as a C=O stretching at 1670 cm^{-1}. A broad stretching band at 3470–3205 cm^{-1} corresponding to one NH_2 and one NH functions in case of **20b,d** or two NH_2 and one NH functions in case of **20c** as well as one CN stretching at 2215–2210 cm^{-1} and one C=O stretching at 1718–1710 cm^{-1} were revealed in the IR spectra of **20b-d**. The ^1H NMR spectrum of **20a** exhibited four D_2O-exchangeable singlets at δ 2.80 (2H), δ 2.90 (2H), δ 4.00 (2H) and δ 8.20 (1H) ppm, corresponding to three NH_2 groups and one NH group, respectively. The presence of a carboxamido function instead of a second carbonitrile group in **20a** confirms the hydrolysis of the carbonitrile function in the assigned reaction sequence. The ^1H NMR spectra of **20c,d** revealed, in addition to the characteristic D_2O-exchangeable singlets of NH_2 and NH protons, an ethyl ester CH_3 triplet and CH_2 quartet at δ 1.39–1.47 (3H) and δ 4.20–4.28 (2H) ppm, respectively, as well as CH_3 singlet at δ 2.40 (3H) ppm in case of compound **20d**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^1H NMR spectra were measured on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed as δ ppm. Analytical data were carried out at the Microanalytical Data Unit at Cairo University.

3,5-Diaminothiophene-2,4-dicarbonitrile (**1**) was prepared through coupling of sulfur with two fold equivalents of malononitrile as described in the literature.[11]

TABLE I Antimicrobial activities of the synthesized compounds in terms of inhibition zones

	Gram Positive Bacteria					*Gram Negative Bacteria*				
Compd No.	*B. Cerceus*	*Staph. aureus*	*Arizona Sp.*	*Citrobactor*	*E. Coli*	*K. Pneumoniae*	*P. aeruginosa*	*P. (Sp.)*	*P (Sp. 2)*	*S. Cerro*
1	+	++	++++	++++	++++	++++	+-	+	++	+++
5a	–	–	–	–	–	–	–	–	–	–
8a	+	++	+	–	++++	–	–	–	–	+-
8b	–	–	–	–	–	–	–	–	–	–
8c	–	++++	+++	–	–	–	–	–	–	–
8d	–	+-	–	+-	–	–	+	–	–	–
11b	+	++	+	–	+	++	–	–	–	+-
13a	–	++++	+++	+++	++++	++++	–	–	–	+++
15b	–	–	–	–	–	–	–	–	–	–
15c	–	–	–	–	–	+++	–	–	–	–
15d	++++	–	+-	–	–	–	–	–	+-	–
17a	–	+-	+	+-	–	–	+	+++	+++	++
17b	–	++++	++++	–	++++	++++	–	–	+-	–
17c	+	++++	++++	+++	++++	++++	+-	–	–	+++

	Gram Positive Bacteria					*Gram Negative Bacteria*				
Compd No.	*B. Cerceus*	*Staph. aureus*	*Arizona Sp.*	*Citrobactor*	*E. Coli*	*K. Pneumoniae*	*P. aeruginosa*	*P. (Sp.)*	*P (Sp. 2)*	*S. Cerro*
17d	–	++++	+++	++	++++	+++	–	–	–	–
21a	–	–	–	–	–	–	–	–	–	–
21b	–	–	–	–	+	–	–	–	–	–
21c	–	–	–	–	–	–	–	–	–	–
21d	–	–	–	–	–	–	–	–	–	–
23a	++	+	++	–	++++	+	–	+	+	++
23b	–	–	–	+-	–	+	–	–	–	–
23c	–	–	–	–	–	–	–	–	–	–
23d	–	–	–	–	–	–	–	–	–	–

No effect = -, Slight effect = +, Moderat effect = ++, Hight effect = +++, Severe effect = ++++; Rating percent control: No effect = 0; Slight effect = 0, 20, 30; Moderate effect = 40, 50, 60; High effect = 70, 80; Severe effect = 90, > 90; Complete effect = 100.

Ethyl 5-cyano-2,4-diaminothiophene-3-carboxylate (2)

Equimolar amounts (0.1 mol) of sulfur, malononitrile and ethyl cyanoacetate in absolute ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml) were heated, under reflux, for 2 h. The solid product formed upon neutralization with cold water containing few drops of HCl was collected by filtration and crystallized from dioxane.

Compound **2**: Yellow crystals, from dioxane, yield 62% (13.08 g), mp 245°C. Analysis for $C_8H_9N_3O_2S$ (211.23): Calcd: C, 45.48; H, 4.29; N, 19.89; S, 15.17 %. Found: C, 45.2; H, 4.1; N, 19.9; S, 15.1 %. R (ν/cm^{-1}): 3450–3240 ($2NH_2$), 2215 (CN), 1712 (C=O). H NMR (δ ppm): 1.23 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 4.46 (s, 2H, NH_2, D_2O-exchangeable), 6.20 (s, 2H, NH_2, D_2O-exchangeable).

4-Carbanilido-3,5-diaminothiophene-2-carbonitrile (3)

Equimolar amounts (0.1 mol) of sulfur, malononitrile and cyanoacetanilide [prepared by adding aniline (1 ml) to ethyl cyanoacetate (1.1 ml) and refluxing for 1 h] in absolute ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml) were heated, under reflux, for 2 h. The solid product formed upon neutralization with cold water containing few drops of HCl was collected by filtration and crystallized from DMF.

Compound **3**: Pale brown crystals, from DMF, yield 72% (18.58 g), mp 172°C. Analysis for $C_{12}H_{10}N_4OS$ (258.29): Calcd : C, 55.80; H, 3.89; N, 21.69; S, 12.41 %. Found: C, 56.0; H, 3.7; N, 21.7; S, 12.3 %. IR (ν/cm^{-1}): 3450–3190 $2NH_2$, NH), 3030 (CH aromatic), 2220 (CN), 1675 C=O). ^{1}H NMR (δ ppm): 4.20 (s, 2H, NH_2, D_2O-exchangeable), 5.50 (s, 2H, NH_2, D_2O-exchangeable), 7.32–7.65 (m, 5H, C_6H_5), 8.51 (s, 1H, NH, D_2O-exchangeable).

3-Amino-5-(benzylideneamino)thiophene-2,4-dicarbonitrile (5a) and 3-Amino-5-(2-Hydroxybenzylideneamino) thiophene-2,4-dicarbonitrile (5b)

General Procedure

A mixture of **1** (0.01 mol) and each of benzaldehyde (**4a**) (0.01 mol) or salicylaldehyde (**4b**) (0.01 mol), in absolute ethanol (30 ml) containing a

catalytic amount of triethylamine (0.5 ml), was heated under reflux for 2 h. The reaction mixture was cooled at room temperature and poured onto water containing few drops of HCl, whereby the solid products, so formed, were filtered off, dried and crystallized from dioxane.

Compound **5a**: Orange crystals, from dioxane, yield 60% (1.51 g), mp 106°C. Analysis for $C_{13}H_8N_4S$ (252.29): Calcd: C, 61.89; H, 3.19; N, 22.20; S, 12.70 %. Found: C, 62.0; H, 3.2; N, 22.2; S, 12.5 %. IR (ν/cm^{-1}): 3425, 3344 (NH_2), 3040 (CH aromatic), 2220, 2215 (2CN), 1632 (C=N).

Compound **5b**: Buff crystals, from dioxane, yield 73% (1.96 g), mp 122°C.

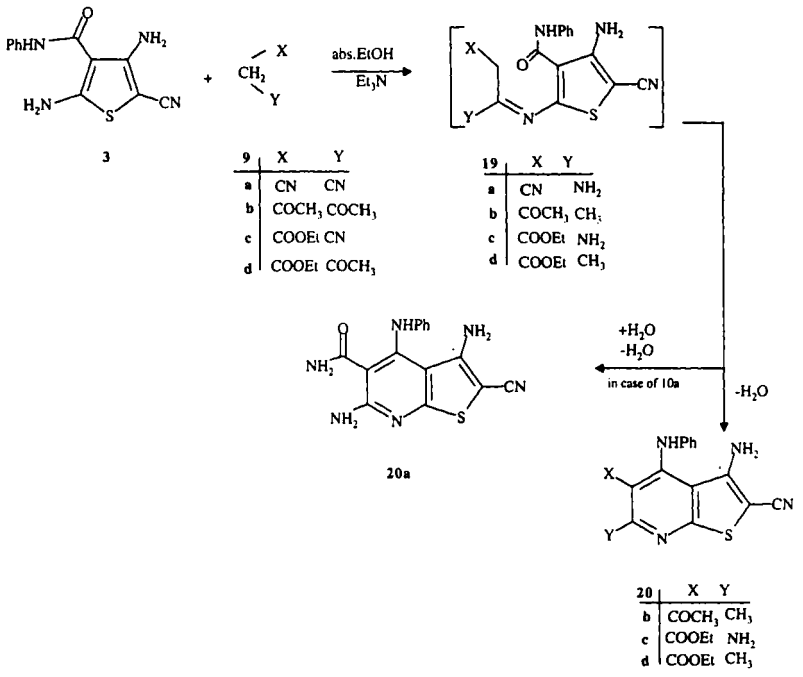
Analysis for $C_{13}H_8N_4OS$ (268.29): Calcd: C, 58.20; H, 3.00; N, 20.88; S, 11.95 %. Found: C, 58.3; H, 2.9; N, 20.9; S, 12.0 %. IR (ν/cm^{-1}): 3560–3350 (OH, NH_2), 3040 (CH aromatic), 2220, 2215 (2CN), 1632 (C=N). ^{1}H NMR δ ppm): 4.79 (s, 2H, NH_2, D_2O-exchangeable), 7.01–7.32 (m, 5H, C_6H_4, CH ylidene), 9.98 (s, 1H, OH, D_2O-exchangeable).

3,4-Diamino-6-phenylthieno[2,3-*b*]pyridine-2,5-dicarbonitrile (8a),6-(2-Chlorophenyl)-3,4-diaminothieno[2,3-*b*]pyridine-2,5-dicarbonitrile (8b), 3,4-Diamino-6-(4-methoxyphenyl)thieno[2,3-*b*] pyridine-2,5-dicarbonitrile (8c) and 3,4-Diamino-6-(2-Furyl)thieno [2,3-*b*]pyridine-2, 5-dicarbonitrile (8d)

General Procedure

A solution of **1** (0.01 mol) in DMF (30 ml) containing each of benzylidenemalononitrile (**6a**) (0.01 mol), 2-chlorobenzylidenemalononitrile (**6b**) (0.01 mol), 4-methoxybenzylidenemalononitrile (**6c**) (0.01 nol) or furfurylidenemalononitrile (**6d**) (0.01 mol) was heated, under reflux, in the presence of triethylamine (0.5 ml) for 3 h. The reaction mixture was then poured onto ice-water mixture and neutralized with dilute HCl. The solid products, so formed, were filtered off and crystallized from the proper solvents.

Compound **8a**: Pale brown crystals, from dioxane, yield 70% (2.04 g), mp 88°C. Analysis for $C_{15}H_9N_5S$ (291.32): Calcd : C, 61.84; H, 3.11; N, 24.03; S, 11.00 %. Found: C, 61.8; H, 2.9; N, 21.0; S, 10.9 %. IR (ν/cm^{-1}): 3450–3235 ($2NH_2$), 3035 (CH aromatic), 2218, 2215 (2CN), 1625 (C=N). ^{1}H NMR (δ ppm): 2.95 (s, 2H, NH_2, D_2O-exchangeable), 3.90 (s, 2H, NH_2, D_2O-exchangeable), 7.15–7.30 (m, 5H, C_6H_5).



SCHEME 4

Compound **8b**: Yellow crystals, from EtOH, yield 74% (2.41 g), mp 100°C. Analysis for $C_{15}H_8ClN_5S$ (325.77): Calcd: C, 55.30; H, 2.47; N, 21.49; S, 9.84 %. Found: C, 55.3; H, 2.5; N, 21.5; S, 9.6 %. IR (ν/cm^{-1}): 3440–3220 ($2NH_2$), 3040 (CH aromatic), 2220, 2215 (2CN), 1635 (C=N). ^{1}H NMR (δ ppm): 2.70 (s, 2H, NH_2, D_2O-exchangeable), 4.00 (s, 2H, NH_2, D_2O-exchangeable), 7.20–7.45 (m, 4H, C_6H_4).

Compound **8c**: Yellowish brown crystals, from dioxane, yield 62% (1.99 g), mp 103°C. Analysis for $C_{16}H_{11}N_5OS$ (321.35): Calcd : C, 59.80; H, 3.44; N, 21.79; S, 9.97 %. Found: C, 59.6; H, 3.5; N, 21.7; S, 10.0 %. IR (ν/cm^{-1}): 3450–3240 ($2NH_2$), 3040 (CH aromatic), 2960, 2875 CH_3), 2215, 2210 (2CN), 1635 (C=N). ^{1}H NMR (δ ppm): 2.81 (s, 2H, NH_2, D_2O-exchangeable), 3.75 (s, 3H, OCH_3), 4.20 (s, 2H, NH_2, D_2O-exchangeable), 7.15–7.90 (m, 4H, C_6H_4).

Compound **8d**: Buff crystals, from DMF, yield 58% (1.63 g), mp 144°C. Analysis for $C_{13}H_7N_5OS$ (281.28): Calcd: C, 55.51; H, 2.50; N, 24.89; S,

1.39 %. Found: C, 55.3; H, 2.5; N, 22.8; S, 11.3 %. IR (ν/cm^{-1}): 3400–3200 ($2NH_2$), 2220, 2215 (2CN),1630 (C=N). ^{1}H NMR (δ ppm): 2.70 (s, 2H, NH_2, D_2O-exchangeable), 4.20 (s, 2H, NH_2, D_2O-exchangeable), 6.17–7.60 (m, 3H, furan).

3-Amino-4-hydroxy-6-phenylthieno[2,3-*b*]pyridine-2,5-dicarbonitrile (13a), 3-amino-4-hydroxy-6-(4-methoxyphenyl)thieno[2,3-*b*] pyridine-2,5-dicarbo-nitrile (13b), 3-amino-6-(2-furyl)-4-hydroxy-thieno[2,3-*b*]pyridine-2,5-dicarbonitrile (13c), 3-amino-5-carbamoyl-6-phenyl-4-(phenylamino)thieno[2,3-*b*]pyridine-2-carbonitrile (18a), 3-amino-5-carbamoyl-6-(4-methoxyphenyl)-4-(phenylamino)thieno[2,3-*b*]-pyridine-2- carbonitrile (18b) and 3-amino-5-carbamoyl-6-(2-furyl)-4-(phenylamino)thieno [2,3-*b*]pyridine-2-carbonitrile (18c)

General Procedure

A mixture of either **2** (0.01 mol) or **3** (0.01 mol) each of benzylidenemalononitrile (**6a**) (0.01 mol), 4-methoxybenzylidenemalononitrile (**6b**) (0.01 mol) or furfurylidenemalononitrile (**6d**) (0.01 mol), in absolute ethanol (30 ml) and in the presence of triethylamine (0.5 ml), was heated under reflux for 3 h. The reaction mixture was cooled at room temperature and poured onto water containing few drops of HCl whereby the solid products, so formed, were filtered off, dried and crystallized from the appropriate solvents.

Compound **13a**: Orange crystals, from EtOH, yield 79% (2.31g), mp 165°C. Analysis for $C_{15}H_8N_4OS$ (292.31): Calcd: C, 61.63; H, 2.75; N, 19.16; S, 10.96 %. Found: C, 61.6; H, 2.5; N, 19.1; S, 1.0 %. IR (ν/cm^{-1}): 3550–3340 (OH, NH_2), 3035 (CH aromatic), 2225, 2220 (2CN), 1635 (C=N). ^{1}H NMR (δ ppm): 4.10 (s, 2H, NH_2, D_2O-exchangeable), 7.18–7.40 (m, 5H, C_6H_5), 10.15 (s, H, OH, D_2O-exchangeable).

Compound **13b**: Reddish brown crystals, from EtOH, yield 78% (2.51 g), mp 150°C. Analysis for $C_{16}H_{10}N_4O_2S$ (322.33): Calcd: C, 59.62; H, 3.12; N, 17.38; S, 9.94 %. Found: C, 59.4; H, 2.9; N, 17.2; S, 9.9 %. IR (ν/cm^{-1}): 3560–3350 (OH, NH_2), 3040 (CH aromatic), 2960, 2875 (CH_3), 2215, 2210 (2CN), 1640 (C=N).

Compound **13c**: Buff crystals, from dioxane, yield 69% (1.95 g), mp 138°C. Analysis for $C_{13}H_6N_4O_2S$ (282.27): Calcd: C, 55.31; H, 2.14; N,

19.84; S, 11.35 %. Found: C, 55.0; H, 2.1; N, 19.6; S, 1.2 %. IR (ν/cm^{-1}): 3530–3320 (OH, NH_2), 2225, 2215 (2CN), 1630 (C=N). ^{1}H NMR (δ ppm): 4.40 (s, 2H, NH_2, D_2O-exchangeable), 6.20–7.72 (m, 3H, furan), 9.20 (s, 1H, OH, D_2O-exchangeable).

Compound **18a**: Brown crystals, from DMF, yield 60% (2.31 g), mp 105°C. Analysis for $C_{21}H_{15}N_5OS$ (385.43): Calcd: C, 65.44; H, 3.91; N, 18.16; S, 8.31 %. Found: C, 65.4; H, 4.0; N, 18.0; S, 8.2 %. IR (ν/cm^{-1}): 3430–3195 ($2NH_2$, NH), 3030 (CH aromatic), 2220 (CN), 1665 (C=O), 1620 (C=N).

Compound **18b**: Red crystals, from dioxane, yield 76% (3.15 g), mp 70°C. Analysis for $C_{22}H_{17}N_5O_2S$ (415.45): Calcd: C, 63.60; H, 4.12; N, 16.85; S %. Found: C, 63.6; H, 3.9; N, 6.5; S, 7.7 %. IR (ν/cm^{-1}): 3420–3190 ($2NH_2$, NH), 3035 (CH aromatic), 2961, 2873 (CH_3), 2225 (CN), 1668 (C=O), 1630 (C=N). ^{1}H NMR (δ ppm): 3.79 (s, 3H, OCH_3), 3.00, 3.90 (2s, 4H, $2NH_2$, D_2O-exchangeable), 7.31–8.20 (m, 9H, C_6H_4, C_6H_5), 9.30 (s, 1H, NH, D_2O-exchangeable).

Compound **18c**: Brown crystals, from dioxane, yield 85% (3.19 g), mp 86°C. Analysis for $C_{19}H_{13}N_5O_2S$ (375.39): Calcd: C, 60.79; H, 3.48; N, 18.65; S, 8.54 %. Found: C, 60.5; H, 3.2; N, 18.6; S, 8.6 %. IR (ν/cm^{-1}): 3440–3200 ($2NH_2$, NH), 3030 (CH aromatic), 2215 (CN), 1660 (C=O), 1625 (C=N). ^{1}H NMR (δ ppm): 2.90, 4.20 (2s, 4H, $2NH_2$, D_2O-exchangeable), 6.10–7.80 (m, 3H, furan), 7.90–8.20 (m, 5H, C_6H_5), 8.61 (s, ^{1}H, NH, D_2O-exchangeable).

3,4,6-Triaminothieno[2,3-*b*]pyridine-2,5-dicarbonitrile (11a), 5-Acetyl-3,4-diamino-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (11b)

General procedure

Equimolar amounts (0.01 mol) of **1** and each of malononitrile (**9a**) or acetylacetone (**9b**), in absolute ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml), were heated under reflux for 2 h. The solid products, formed upon dilution with water containing few drops of HCl, were isolated by filtration and crystallized from the porper solvents.

Compound **11a**: Brown crystals, from DMF, yield 69% (1.59 g), mp 244°C. Analysis for $C_9H_6N_6S$ (230.24): Calcd: C, 46.95; H, 2.62; N, 36.49; S, 13.92 %. Found: C, 47.0; H, 2.5; N, 36.2; S, 13.9 %. IR (ν/cm^{-1}): 3495–3200 ($3NH_2$), 2225, 2220 (2CN), 1640 C=N). ^{1}H NMR (δ ppm):

2.76 (s, 2H, NH_2, D_2O-exchangeable), 3.12 (s, 2H, NH_2, D_2O-exchangeable), 4.30 (s, 2H, NH_2, D_2O-exchangeable).

Compound **11b**: Pale yellow crystals, from EtOH, yield 64% (1.57 g), mp 116°C. Analysis for $C_{11}H_{10}N_4OS$ (246.28): Calcd: C, 53.64; H, 4.08; N, 22.74; S, 13.01 %. Found: C, 53.5; H, 3.9; N, 22.7; S, 12.9 %. IR (ν/cm^{-1}): 3400–3250 ($2NH_2$), 2965, 2872 (CH_3), 2215 (CN), 1710 (C=O), 1635 (C=N). ^{1}H NMR (δ ppm): 2.58, 2.95 (2s, 6H, $2CH_3$), 3.28 (s, 2H, NH_2, D_2O-exchangeable), 3.95 (s, 2H, NH_2, D_2O-exchangeable).

3,6-Diamino-4-hydroxythieno[2,3-*b*]pyridine-2,5-dicarbonitrile (16a), 5-acetyl-3-amino-4-hydroxy-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (16b), 3,6-diamino-5-ethoxycarbonyl)-4-hydroxythieno [2,3-*b*]pyridine-2-carbo-nitrile (16c), 3-amino-5-ethoxycarbonyl)-4-hydroxy-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (16d), 5-carbamoyl-3,6-diamino-4-(phenylamino)thieno[2,3-*b*]pyridine-2-carbo-nitrile (20a). 5-Acetyl-3-amino-6-methyl-4-(phenylamino) thieno[2,3-*b*]pyridine-2-carbo-nitrile (20b), 3,6-diamino-5-(ethoxycarbonyl)-4-(phenylamino)thieno[2,3-*b*]pyridine-2-carbonitrile (20c) and 3-amino-5-(ethoxycarbonyl)-6-methyl-4-(phenylamino)-Thieno[2,3-*b*]-pyridine-2-carbonitrile (20d)

General procedure

To a solution of either **2** (0.01 mol) or **3** (0.01 mol), in absolute ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml), each of malononitrile (**9a**) (0.01 mol), acetylacetone (**9b**) (0.01 mol), ethyl cyanoacetate (**9c**) (0.01 mol) or ethyl acetoacetate (**9d**) (0.01 mol) was added. The reaction mixture was heated, under reflux, for 2 h and then neutralized by pouring onto ice-water mixture containing few drops of HCl. The solid products were collected by filtration and crystallized from the proper solvents.

Compound **16a**: Yellowish brown crystals, from DMF, yield 68% (1.57 g), mp 186°C. Analysis for $C_9H_5N_5OS$ (231.23): Calcd: C, 46.75; H, 2.17; N, 30.28; S, 13.8 %. Found: C, 46.5; H, 2.2; N, 30.0; S, 13.6 %. IR (ν/cm^{-1}): 3540–3330 (OH, $2NH_2$), 2215, 2210 (2CN), 1632 (C=N). ^{1}H NMR (δ ppm): 2.50 (s, 2H, NH_2, D_2O-exchangeable), 3.20 (s, 2H, NH_2, D_2O-exchangeable), 11.20 (s, 1H, OH, D_2O-exchangeable).

Compound **16b**: Buff crystals, from dioxane, yield 40% (0.99 g), mp 230°C. Analysis for $C_{11}H_9N_3O_2S$ (247.26): Calcd : C, 53.43; H, 3.66; N, 16.99; S, 12.96 %. Found: C, 53.1; H, 3.5; N, 17.0; S, 13.1 %. IR (ν/cm^{-1}): 3520–3315 (OH, NH_2), 2965, 2870 (CH_3), 2220 (CN), 1700 (C=O), 1625 (C=N). ^{1}H NMR (δ ppm): 2.45 (s, 3H, CH_3), 2.64 (s, 3H, CH_3CO), 3.95 (s, 2H, NH_2, D_2O-exchangeable), 11.30 (s, 1H, OH, D_2O-exchangeable).

Compound **16c**: Pale yellow crystals, from DMF, yield 53% (1.47 g), mp 140°C. Analysis for $C_{11}H_{10}N_4O_3S$ (278.28): Calcd: C, 47.47; H, 3.61; N, 20.13; S, 11.52 %. Found: C, 47.5; H, 3.4; N, 20.0; S, 11.2 %. IR (ν/cm^{-1}): 3550–3320 (OH, 2NH_2), 2960–2859 (CH_3, CH_2), 2210 (CN), 1715 (C=O), 1630 (C=N). ^{1}H NMR (δ ppm): 1.39 (t, 3H, CH_3), 2.90 (s, 2H, NH_2, D_2O-exchangeable), 3.20 (s, 2H, NH_2, D_2O-exchangeable), 4.23 (q, 2H, CH_2), 10.85 (s, 1H, OH, D_2O-exchangeable).

Compound **16d**: Orange crystals, from dioxane, yield 47% (1.29 g), mp 98°C. Analysis for $C_{12}H_{11}N_3O_3S$ (277.29): Calcd: C, 51.97; H, 3.99; N, 15.15; S, 11.56 %. Found: C, 52.1; H, 3.8; N, 5.1; S, 1.7%. IR (ν/cm^{-1}): 3580–3340 (OH, NH_2), 2960–2858 (CH_3, CH_2), 2220 (CN), 1710 (C=O), 1625 (C=N).

Compound **20a**: Reddish brown crystals, from DMF, yield 60% (1.94 g), mp 168°C. Analysis or $C_{15}H_{12}N_6OS$ (324.56): Calcd: C, 55.54; H, 3.72; N, 25.90; S, 9.88 %. Found: C, 55.3; H, 3.5; N, 26.0; S, 9.7 %. IR (ν/cm^{-1}): 3500–3201 (3NH_2, NH), 3040 (CH aromatic), 2225 (CN), 1670 (C=O), 1630 (C=N). ^{1}H NMR (δ ppm): 2.80, 2.90, 4.00 (3s, 6H, 3NH_2, D_2O-exchangeable), 7.30–7.69 (m, 5H, C_6H_5), 8.20 (s, 1H, NH, D_2O-exchangeable).

Compound **20b**: Pale brown crystals, from dioxane, yield 52% (1.67 g), mp 102°C. Analysis for $C_{17}H_{15}N_4OS$ (322.37): Calcd: C, 63.33; H, 4.37; N, 17.37; S, 9.94 %. Found: C, 63.1; H, 4.2; N, 17.3; S, 9.8 %. IR (ν/cm^{-1}): 3450–3210 (NH_2, NH), 3045 (CH aromatic), 2966, 2870 (CH_3), 2210 CN), 1710 (C=O), 1640 (C=N).

Compound **20c**: Buff crystals, from DMF, yield 67% (2.37 g), mp 108°C. Analysis for $C_{17}H_{15}N_5O_2S$ (353.38): Calcd : C, 57.78; H, 4.27; N, 19.81; S, 9.07 %. Found: C, 57.8; H, 4.0; N, 19.5; S, 9.0 %. IR (ν/cm^{-1}): 3470–3205 (2NH_2, NH), 3030 (CH aromatic), 2960–2859 (CH_3, CH_2), 2215 (CN), 1715 (C=O), 1635 (C=N). ^{1}H NMR (δ ppm): 1.39 (t, 3H, CH_3), 2.90, 3.90, (2s, 4H, 2NH_2, D_2O-exchangeable), 4.28 (q, 2H, CH_2), 7.35–7.70 (m, 5H, C_6H_5), 8.20 (s, 1H, NH, D_2O-exchangeable).

Compound **20d**: Yellow crystals, from DMF, yield 61% (2.15 g), mp 93°C. Analysis for $C_{18}H_{16}N_4O_2S$ (352.40): Calcd: C, 61.35; H, 4.57; N, 15.89; S, 9.09 %. Found: C, 61.1; H, 4.5; N, 15.7; S, 8.9 %. IR (ν/cm^{-1}): 3450–3214 (NH_2, NH), 3050 (CH aromatic), 2963–2857 (CH_3, CH_2), 2210 (CN), 1718 (C=O), 1630 (C=N). ^{1}H NMR (δ ppm): 1.47 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.00 (s, 2H, NH_2, D_2O-exchangeable), 4.20 (q, 2H, CH_2), 7.30–7.69 (m, 5H, C_6H_5), 8.20 (s, lH, NH, D_2O-exchangeable).

Biological activity

The diverse biological activities of azole and azine derivatives promoted our attention to test and study the biological activities of some newly synthesized products. The bactericidal and antifungal activities[12,13] were studied. A disc of blotting paper is impregnated with a known volume and appropriate concentration of a compound, placed on a sensitivity testing agar plate which inoculated with the test organism. The compound diffuses from the disc into the medium. The culture was examined for areas of no growth around the disc (zones of inhibition) after overnight incubation. Bacterial strains sensitive to a compound are inhibited at a distance from the disc whereas resistant strains grow up to the edge of the disc.

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