Synthesis of New Derivatives of Thieno[2,3-*b*]pyridine Fused with Octyl Ring

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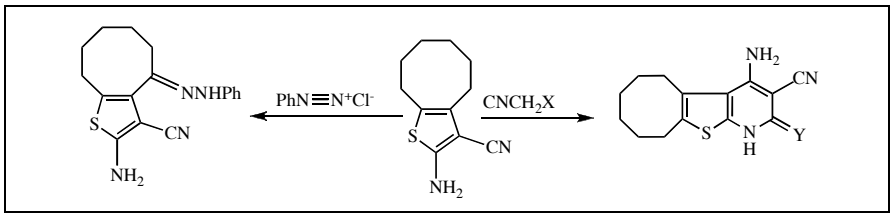

Derivatives of thiophene, thieno[2,3-*b*]pyridine, thieno[5',4':4,5]pyrimido[3,2-*a*]pyridine and thiepine fused with octyl ring have been synthesized and tested for antimicrobial and antifungal activities. The structure of the newly synthesized compounds have been established on the basis of their analytical and spectral data.

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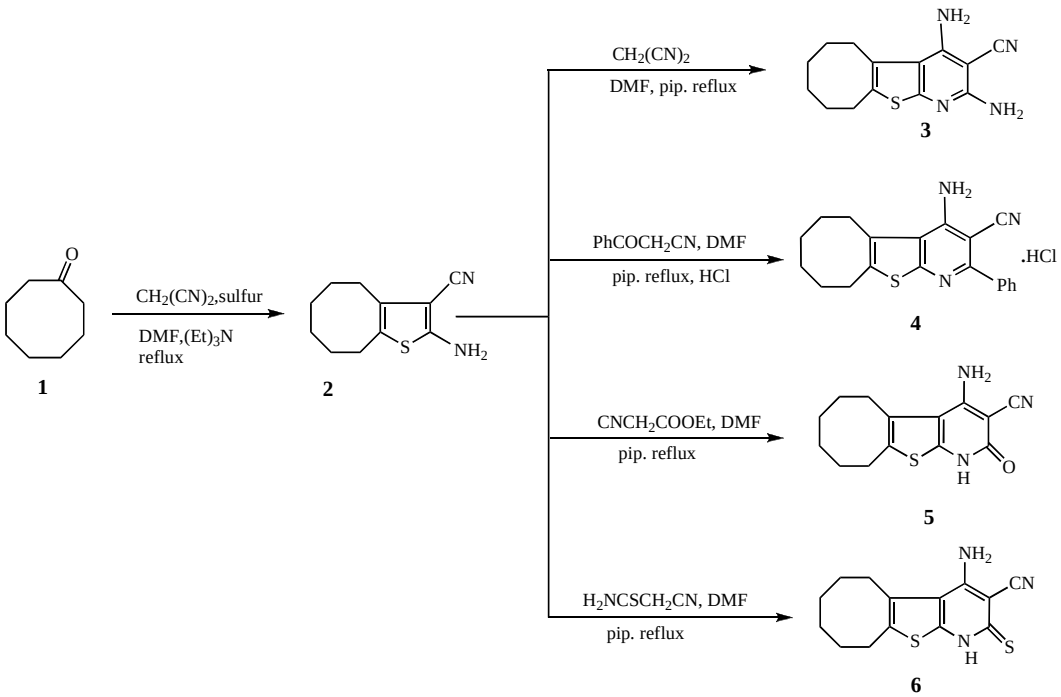
INTRODUCTION

Pharmacological studies of the thieno[2,3-*b*]pyridine derivatives have been shown to posses a variety of pharmacological activities such as antibacterial [1,2], anti-hypertensive and vasodilator activities [3]. Some thieno-[2,3-*b*]pyridine derivatives are useful as gonadotropin-releasing hormone antagonists [4-9]. Others were prepared as anti-inflammatory agents, particularly for treating arthritis and bone resorption inhibiting agents [10]. It was interesting to study unreported tri- and tetra-cyclic compounds containing nitrogen and sulfur heterocycles in the hope of obtaining compounds of potential antimicrobial and antifungal activities. To prepare this novel class of compounds we used new 2-aminocycloocta[*b*]thiophene-3-carbonitrile as the key intermediate.

RESULTS AND DISCUSSION

The key intermediate **2** used in our experiments has been prepared according to Gewald's reaction [11] by refluxing the cyclooctanone **1** with malononitrile in *N*,*N*-dimethylformamide (DMF) in the presence of elemental

Scheme 1



sulfur and a catalytaic amount of triethylamine. The structure of **2** was established on the basis of spectral data and formula confirm by elemental analysis. Thus, the ir spectrum of compound **2** showed a strong absorption band at ν 2195, 3428 and 3333 cm^{-1} corresponding to nitrile and amino groups, respectively. The absence of the carbonyl group absorption, in the ir spectrum, indicates that the carbonyl group is involved in the reaction.

The reactivity of the thiophene **2** toward active methylene nitriles was investigated. Thus, treatment of **2** with malononitrile in refluxing DMF and in presence of a catalytic amount of piperidine gave the 2,4-diaminocycloocta[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile **3** (Scheme 1). The structure of the latter product was established on the basis of its elemental analysis and spectral data. Thus, the ^1H nmr spectrum of the reaction product **3** revealed, besides the aliphatic multiplet, two types of D_2O-exchangeable protons at δ 3.53 and 7.95 ppm for the two amino groups.

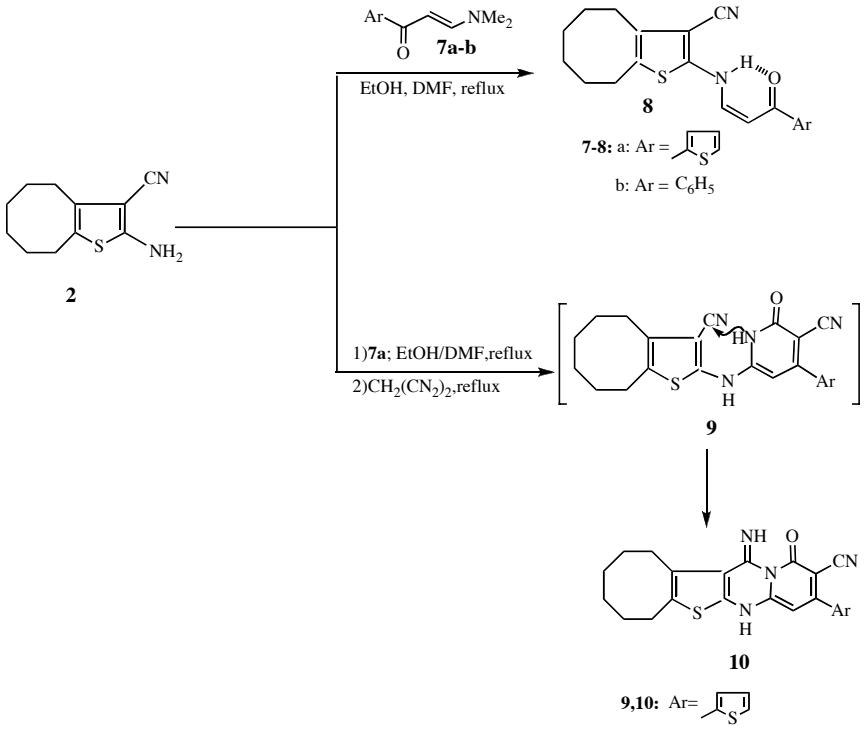
Treatment of compound **2** with benzoylacetonitrile in DMF at refluxed afforded the corresponding 4-amino-2-phenylcycloocta[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile hydrochloride **4** in good yield. The structure of the latter product was established on the basis of its spectral data and molecular analysis. Thus the ir spectrum of the reaction product showed an absorption bands at 3423, 3334 cm^{-1} for the amino group in addition to a strong absorption band at 2195 cm^{-1} for the cyano group.

In a similar manner, treatment of compound **2** with ethyl cyanoacetate or cyanothioacetamide under refluxing in DMF and the presence of a catalytic amount of piperidine gave a brown crystalline product identified as 4-amino-2-oxo-1*H*,2*H*-cycloocta[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile **5** and 4-amino-2-thioxo-1*H*,2*H*-cycloocta-[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile **6**, respectively in good yield similar to that which recently has been reported from our laboratories [12]. The structures of **5** and **6** were established *via* their analytical and spectroscopic data. The mass spectrum of **5** revealed a molecular ion peak *m/z* at 273. The ^1H nmr spectrum of the reaction product showed in addition to the aliphatic signals, two singlet signal at δ 6.88 and 11.97 ppm assigned to the NH_2 and NH group. The latter two signals underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide.

On the other hand, treatment of **2** with enaminones **7a-b** afforded the corresponding enaminones **8a-b** (*cf.* Scheme 2). The formation of **8a-b** are assumed to proceed *via* addition of amino group in compound **2** to the enamino double bond of **7** followed by elimination of a dimethylamine molecule. The structure of products **8a-b** were assigned as the *Z*-form based on ^1H nmr which revealed olefinic protons as two doublets at δ 6.97 and 7.66 ppm with *J*=10 Hz as required for such *Z*-coupled protons. Predominance of the *Z* form rather than the *E* form is attributed to fixation through hydrogen bonding. The mass spectrum of **8b** revealed a molecular ion peak *m/z* at 336 (Scheme 2).

Compound **10** could be obtained *in situ via* a one step process by the treatment of **2** with 3-dimethylamino-1-(2'-

Scheme 2



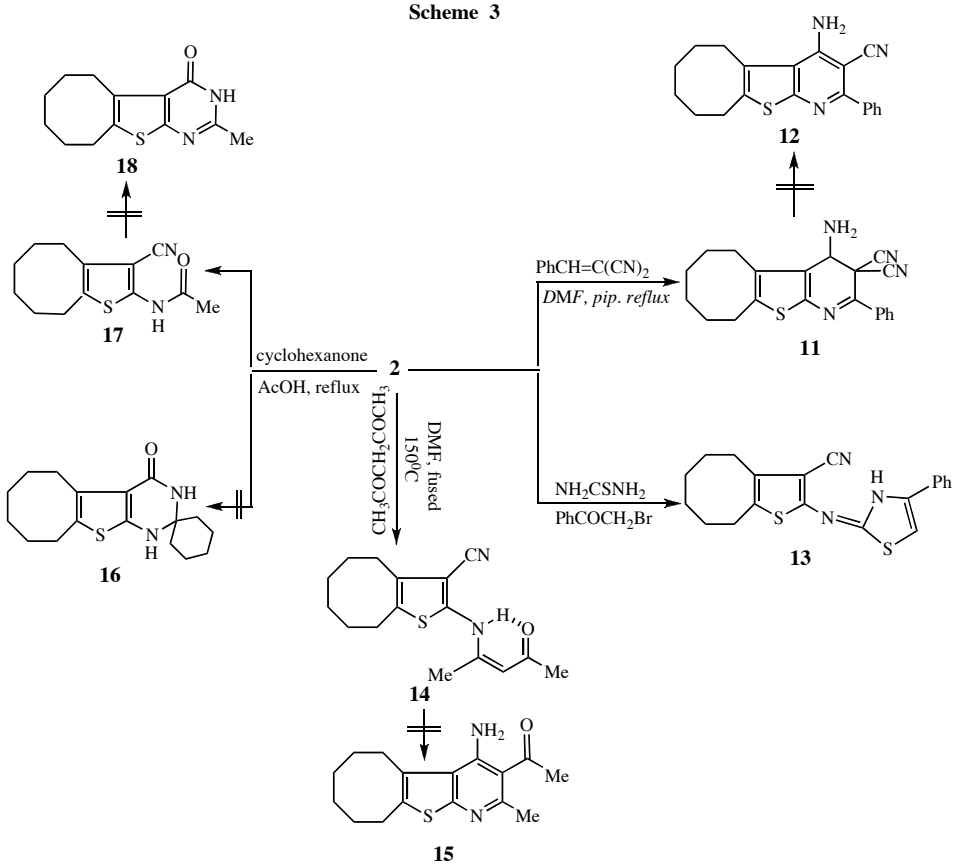
thienyl)-2-propenone **7a** in refluxing ethanol and DMF followed by treatment of the reaction mixture with malononitrile. The formation of **10** is assumed to proaceed *via* non-isolated intermediate **9** followed by an intramolecular cyclization under these reaction conditions to afford theinopyrimidopyridine derivative **10**. Analytical and spectral data are consistent with the assigned structure (see Experimental).

Treatment of compound **2** with benzylidenemalononitrile in refluxing DMF and in the presence of a catalytic amount of piperidine afforded 3,4-dihydrothieno[2,3-*b*]-pyridine derivative **11** in good yield. The structure of the latter compound was confirmed on the basis of elemental analysis and spectral data. The mass spectrum of **11** revealed a molecular ion peak with *m/z* 360. Compound **11** is assumed to take place *via* initial Michael addition of the amino group in compound **2** to an activated double bond in benzylidenemalononitrile followed by cyclization to afford **11**. The formed adduct did not aromatize by losing hydrogen cyanide. Perhaps in this case,**11** is a more stable product than the product that would be obtained by elimination of hydrogen cyanide **12**. Similar dihydrothieno[2,3-*b*]pyridine formations have been reported in Ref. [12].

Thiazol-2-ylidene derivative **13** could be obtained in *situ via* a one step process by the treatment of **2** with thiourea in refluxing ethanol and DMF followed by treatment of the reaction mixture with phenacyl bromide. The structure was confirmed by analytical and spectral data. The ir spectrum revealed the disappearance of the bands corresponding the 3428 and 3333 cm^{-1} corresponding to the NH_2 group. The ^1H nmr spectrum also lacked the NH_2 signal and showed a multiplet at δ 7.32 - 7.89 ppm for aromatic protons in addition to a new singlet one at δ 7.23 ppm which integrates for one proton and is attributed to the 5-H of the thiazoline ring proton and other resonance at δ 11.92 ppm was assigned to the NH proton. The latter signal underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide. Notably a literature survey revealed that thiazoline derivatives are biological interesting candidates [13-14].

Upon fusion of **2** with acetylacetone, a crystalline-brown colored product was formed. The mass spectrum revealed a molecular ion peak with *m/z* 288. Although the thieno[2,3-*b*]pyridine derivative **15** would seem to be a reasonable possible structure, the 2-(4'-oxo-2'-penten-2-yl)-aminocycloocta[*b*]thiophene-3-carbonitrile **14** was actually assigned for this product on the basis of ir and ^1H nmr spectra. The ir spectrum for **14** revealed the presence of cyano and carbonyl absorption bands at ν_{max} 2195 and 1665 cm^{-1}, respectively. The lower frequency of carbonyl group attributed to both hydrogen bonding and to the

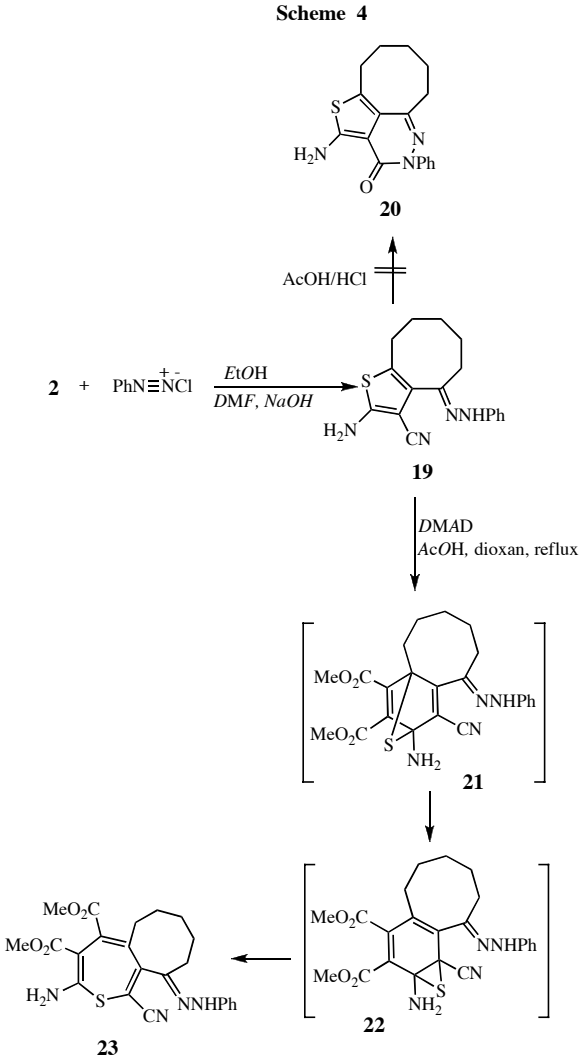
Scheme 3



conjugated double bond readily allowed for the exclusion of structure **15**. In an attempt to obtain the thieno[2,3-*b*]pyridine derivative **15**, compound **14** was subjected to reflux for a greater length of time, however, again it was shown to be unsuccessful as the cyano absorption band was observed in the ir spectrum.

Heating compound **2** with cyclohexanone under refluxed in the presence of acetic acid afforded a product with the potential structure *N*-acetamido derivative **17** rather than spiro compound **16**. The structural assignment is based on analytical data. The presence of cyano absorption in the ir spectrum at ν_{max} 2219 cm^{-1} which readily excluded the possibility of **16**. Again, compound **17** was refluxed for a greater length of time in an attempt to obtain the thienopyrimidine derivative **18**, however again it was found to be unsuccessful as the cyano absorption band was observed in the ir spectrum (Scheme 3).

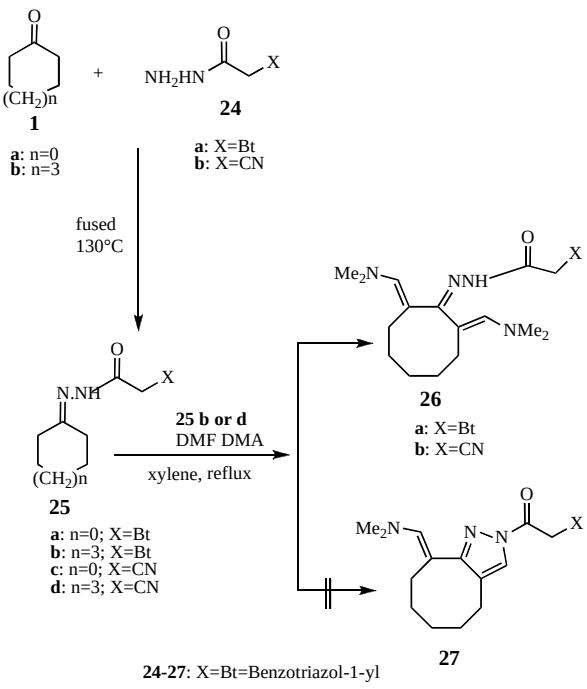
Scheme 4



Treatment of **2** with benzenediazonium chloride in strong basic medium furnished a single product, identified as acyclic hydrazone derivative **19** in good yield. In an attempt to cyclized **19** to the thienopyridazinone derivative **20** upon refluxing in acetic acid and hydrochloric acid mixture was unsuccessful [15]. The reactivity of the acyclic hydrazone **19** toward dimethyl-acetylene dicarboxylate DMAD was investigated. Thus treatment of **19** with DMAD in a mixture of acetic acid and dioxan afforded the thiepine derivative **23** in good yield. The latter compound is believed to be formed *via* intermediates **21** and **22** (*cf.* Scheme 4). Similar formation of thiepine has been reported from our laboratories [16-18] as well as Dopp *et al*. [19]. The structure of the isolated product **23** was confirmed on the basis of elemental analysis and spectral data.

Upon fusion either of cyclohexanone **1a** or cyclo-octanone **1b** with each of 1*H*-benzotriazol-1-yl acetic acid hydrazine **24a** or cyano acetic acid hydrazine **24b** at 130°C afforded the corresponding hydrazone **25a-d** in good yield. Structures **25a-d** were established on the basis of their elemental analysis and spectral data. Treatment of each **25b** or **25d** with dimethylformamide dimethyl-acetal (DMF DMA) in dry xylene at reflux, afforded the enaminones **26a-b** in good yield and not the prazolo derivative **27**. The proposed structure of enaminone was confirmed based on elemental analysis (Scheme 5).

Scheme 5



Biological Activity. The biological activities of some of the newly synthesized compounds were screened for antifungal activity against *Aspergillus niger* and *Penicillium sp* while the antibacterial activity was tested against *Escherichia coli*, *Staphylococcus aureas* and *Saccharomyces cerivisiae*. Most of the test sample showed bacterial and fungicidal activity (Table 1).

Table 1

In *vitro* antimicrobial and fungicidal activities [a] of some newly synthesized compounds [b].

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Saccharomyces cerivisiae*	*Aspergillus niger*	*Penicillium sp*
2	6.0	8.0	15.0	-	-
4	10.0	7.0	-	3.0	-
6	9.0	1.0	9.0	-	-
10	3.0	3.0	-	-	-
25a	7.0	9.0	-	-	-
25b	7.0	8.0	2.0	-	-

[a] Diameter (in mm) of growth inhibition zones; [b] The data expected by the mean.

EXPERIMENTAL

All melting points are uncorrected. The 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 Brucker 400 MHz spectrometer in DMSO-d_6 or *CDCl$_3$* as solvent using TMS as internal standard, δ TMS = 0.00 ppm. Mass spectra were measured on GC/MS VS Autospec Q. Microanalyses were performed on a CHNS-LECO 932 analyzer. Abbreviation: *Et*OH = ethanol, *Et$_3$*N = triethylamine, DMF = *N*,*N*-dimethylformamide, DMSO-d_6 = dimethyl-d_6-sulfoxide, TMS = tetramethylsilane, DMA DMF = *N*,*N*-dimethylformamide dimethylacetal; DMAD = dimethylacetylene dicarboxylate.

2-Amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (2). A mixture of **1** (1.32 g, 10 mmoles), malononitrile (0.66 g, 10 mmoles) and elemental sulfur (0.32 g, 10 mmoles) in DMF (30 mL) containing *Et$_3$*N (1.0 mL) was heated under refluxed for 6 hours. The reaction mixture was left to cool at room temperature and then pour onto ice cold water. The solid product, so formed, was collected by filtration and recrystallized from *Et*OH as brown crystal, 1.46 g (71%), mp 81-820C; ir: ν 3428, 3333 (NH_2), 2924, 2846 (CH_2), 2195 (CN), 1620 (C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.15-1.51 (m, 8H, 5-, 6-, 7-. and 8-H), 2.47 (t, 2H, CH_2, *J*=5 Hz), 2.55 (t, 2H, CH_2, *J*=5 Hz), 6.84 ppm (br.s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 26.0, 26.1, 26.3, 26.4, 30.5, 36.1 (6CH_2), 115.8, 117.4, 126.4, 134.9, 163.3 ppm (thiophene carbons & CN). *Anal*. Calcd. for $C_{11}H_{14}N_2S$ (206.24): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.30; H, 6.82; N, 13.38.

2,4-Diamino-5,6,7,8,9,10-hexahydrocycloocta[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile (3). A mixture of **2** (2.06 g, 10 mmoles) and malononitrile (0.66 g, 10 mmoles) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 3 hours. The reaction was left to cool at room temperature, then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from *Et*OH as brown crystal, 1.60 g (59%), mp. 90-92°C; ir: ν 3431-3335 (2NH_2), 2925, 2848 (CH_2), 2194 (CN), 1619 (C=N) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.25-1.50 (m, 8H, 6-, 7-, 8-, and 9-H), 2.47 (t, 2H, CH_2, *J*=4 Hz), 2.56 (t, 2H, CH_2, *J*=4 Hz), 3.53 (br.s, 2H, NH_2, D_2O exchangeable), 7.95 ppm (br.s, 2H, NH_2, D_2O exchangeable). *Anal*. Calcd. for $C_{14}H_{16}N_4S$ (272.30): C, 61.76; H, 5.92; N, 20.58. Found: C, 61.72; H, 5.78; N, 20.34.

4-Amino-2-phenyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]-thieno[2,3-*b*]pyridine-3-carbonitrile hydrochloride (4). A mixture of **2** (2.06 g, 10 mmoles) and benzoylacetonitrile (1.45 g, 10 mmoles) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 3 hours. The reaction was left to cool at room temperature, then poured onto ice-cold water and neutralized with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from *Et*OH as brown crystal, 2.69 g (73%), mp. 103-105°C; ir: ν 3428, 3334 (NH_2), 2925, 2847 (CH_2), 2195 (CN), 1619(C=N) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.38-1.52 (m, 8H, 6-, 7-, 8-, and 9-H), 2.48 (t, 2H, CH_2, *J*=5 Hz), 2.55 (t, 2H, CH_2, *J*=5 Hz), 6.87 (br.s, 2H, NH_2), 7.49-7.95 ppm (m, 5H, phenyl protons). *Anal*. Calcd. for $C_{20}H_{20}ClN_3S$ (369.91): C, 64.94; H, 5.44; N, 11.35. Found: C, 64.85; H, 5.32; N, 11.26.

4-Amino-2-oxo-1*H*,2*H*-5,6,7,8,9,10-hexahydrocycloocta[*b*]-thieno[2,3-*b*]pyridine-3-carbonitrile (5). A mixture of **2** (2.06 g, 10 mmoles) and ethyl cyanoacetate (1.13 g, 10 mmoles) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 3 hours. The reaction mixture was left to cool at room temperature, then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from *Et*OH as brown crystal, 1.99 g (73%), mp 93-95 °C; ir: ν 3427, 3333 (NH_2), 3218 (NH), 2924, 2848 (CH_2), 2195 (CN), 1620 (CO) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 1.34-1.52 (m, 8H, 6-, 7-, 8-, and 9-H), 2.45-2.54 (m, 4H, 5- and 10-H), 6.88 (br.s, 2H, NH_2, D_2O exchangeable), 11.97 ppm (br.s, 1H, NH, D_2O exchangeable); ^{13}C nmr (DMSO-d_6): δ 25.9, 26.1, 26.3, 26.4, 30.6, 32.1 (6CH_2), 116.4, 117.5, 119.8, 131.3, 134.9, 146.2, 162.4 (aromatic carbons & CN), 163.3 (CO) ppm; ms: *m/z* 273 (M^+). *Anal*. Calcd. for $C_{14}H_{15}N_3OS$ (273.27): C, 61.53; H, 5.53; N, 15.37. Found: C, 61.34; H, 5.23; N, 15.33.

4-Amino-2-thioxo-1*H*,2*H*-5,6,7,8,9,10-hexahydrocycloocta-[*b*]thieno[2,3-*b*]pyridine-3-carbonitrile (6). A mixture of **2** (2.06 g, 10 mmoles) and cyanothioacetamide (1.00 g, 10 mmoles) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 3 hours. The reaction mixture was left to cool at room temperature, then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from *EtOH* as brown crystal, 2.19 g (76%), mp 130-132 °C. ir: ν 3427, 3333 (NH_2), 2923, 2847 (CH_2), 2195 (CN) cm^{-1}; ^{1}H

nmr (DMSO-d_6): δ 1.33-1.52 (m, 8H, 6-, 7-, 8-, and 9-H), 2.47(t, 2H, CH_2, *J*=5 Hz), 2.55 (t, 2H, CH_2, *J*=5Hz), 6.88 (br.s, 2H, NH_2, D_2O exchangeable), 11.9 ppm (br.s, 2H, NH, D_2O exchangeable). *Anal.* Calcd. For $C_{14}H_{15}N_3S_2$ (289.28): C, 58.12; H, 5.23; N, 14.53. Found: C, 58.25; H, 5.27; N, 14.29.

General Procedure for the Preparation 8a-b. A mixture of **2** (2.06 g, 10 mmoles) and either of each **7a** (1.81 g, 10 mmoles) or **7b** (1.75 g, 10 mmoles) in a mixture of EtOH (20 mL) and DMF (10 mL) was refluxed for 3 hours. The reaction was left to cool at room temperature. The solid product, so formed, was collected by filtration and reacrystallized from a mixture of EtOH/DMF (2:1).

2-[3'-Oxo-3'-(2-thienyl)propenyl]amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (8a). This compound was obtained as brown crystal, 2.20 g (71%), mp. 143-145 °C; ir: ν 3427-3215 (NH), 2923, 2849 (CH_2), 2195 (CN), 1623 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.36 – 1.56 (m, 8H, 5-, 6-, 7-, and 8-H), 2.62-2.65 (m, 4H, 4- and 9-H), 6.97 (d, 1H, olefinic proton, *J*=9 Hz), 7.66 (d, 1H, olefinic proton, *J*=9 Hz), 7.23-7.96 (m, 3H, thienyl protons), 11.03 ppm (br.s, 1H, NH). *Anal.* Calcd. for $C_{18}H_{18}N_2S_2O$ (342.36): C, 63.15; H, 5.30; N, 8.18. Found: C, 63.14; H, 5.10; N, 8.38.

2-[3'-Oxo-3'-phenylpropenyl]amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (8b). This compound was obtained as brown crystal; 2.28 g (68%), mp. 155-157°C; ir: ν 3333-3215 (NH), 2925, 2849 (CH_2), 2207 (CN), 1633 (CO)cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.06-1.60 (m, 8H, 5-, 6-, 7-, and 8-H), 2.65-2.77 (m, 4H, 4- and 9-H), 6.97 (d, 1H, olefinic proton, *J*=10 Hz), 7.56 (d, 1H, olefinic proton, *J*=10 Hz), 7.51-7.99 (m, 5H, phenyl protons), 11.03 ppm (br.s, 1H, NH); ms: *m/z* 336 (M^+). *Anal.* Calcd. for $C_{20}H_{20}N_2SO$ (336.36): C, 71.41; H, 5.99; N, 8.32. Found: C, 71.32; H, 5.71; N, 8.21.

13-Imino-1-oxo-3-(2-thienyl)-1*H*,5*H*,13*H*-7,8,9,10,11,12-hexahydrocycloocta[*b*]thieno[5',4':4,5]pyrimido[3,2-*a*]pyridine-2-carbonitrile (10). A solution of **2** (2.06 g, 10 mmoles) and **7a** (1.81 g, 10 mmoles) in a mixture of *Et*OH (20 mL) and DMF (10 mL) was refluxed for 3 hours. To the reaction mixture malononitrile (0.66 g, 10 mmoles) was added and refluxed for 3 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 crystal, 2.35 (63%), mp 90-92°C; ir: ν 3401-3193 (2NH), 2922, 2849 (CH_2), 2196 (CN), 1647 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.03-1.53 (m, 8H, 8-, 9-, 10- and 11-H), 2.47-2.56 (m, 4H, 7- and 12-H), 7.17-7.77 (m, 3H, thienyl protons), 8.10 (s, 1H, 4-H pyridine proton), 11.02 (s, 1H, NH, D_2O-exchangeable), 12.47 ppm (s, 1H, NH, D_2O-exchangeable); ^{13}C nmr (DMSO-d_6); δ 25.86, 25.96, 26.05, 26.41, 30.26, 32.17 ($6CH_2$), 117.35, 119.66, 120.23, 128.84, 129.97, 130.32, 131.76, 133.62, 134.39, 137.00, 144.02, 153.89, 159.04, 163.72, 165.94 ppm (aromatic carbons, CO & CN). *Anal.* Calcd. for $C_{21}H_{18}N_4S_2O$ (406.39): C, 62.06; H, 4.46; N, 13.79. Found: C, 61.86; H, 4.46; N, 13.82.

4-Amino-3*H*,4*H*-5,6,7,8,9,10-hexahydrocycloocta[*b*]thieno-[2,3-*b*]pyridine-3,3-dicarbonitrile (11). A mixture of **2** (2.06 g, 10 mmol) and benzylidenemalononitrile (1.54 g, 10 mmol) in DMF (20 mL)containing piperidine (1.0 mL) was refluxed for 5 hours. The reaction mixture was left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from DMF as brown crystal, 2.30 g (64%), mp. 132-134°C; ir: ν 3336, 3206 (NH_2), 2923, 2823 (CH_2), 2199 (2CN), 1623 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.34-1.63 (m, 8H, 6-, 7-, 8-, and 9-H), 2.46 (s, 1H, 4-H), 2.55 (t, 2H, CH_2, *J*=5 Hz), 2.73 (t, 2H, CH_2, *J*=5 Hz), 7.44-7.97 (m, 5H, phenyl protons), 8.66 ppm (br.s, 2H, NH_2); ms: *m/z* 360 (M^+). *Anal.* Calcd. for $C_{21}H_{20}N_4S$ (360.48): C, 69.97; H, 5.59; N, 15.54. Found: C, 69.88; H, 5.49; N, 15.32.

2-(2',3'-Dihydro-4'-phenylthiazol-2'-ylidene)amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (13). A solution of **2** (2.06 g, 10 mmoles) and thiourea (0.76 g, 10 mmoles) in a mixture of DMF (20 mL) and *Et*OH (10 mL) was refluxed for 3 hours. To the reaction mixture, phenacyl bromide (1.99 g, 10 mmoles) was added and refluxed for 1 hour, then allowed to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from a mixture of *Et*OH/DMF (1:2) as brown crystal, 2.15 g (59%), mp. 80-82°C; ir: ν 3429-3216 (NH), 2924, 2848 (CH_2), 2195 (CN), 1620(C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.03-1.42 (m, 8H, 5-, 6-, 7-, and 8-H), 2.39-2.45 (m, 4H, 4- and 9-H), 7.23 (s, 1H, 5'-H thiazoline proton), 7.32-7.89 (m. 5H, phenyl protons), 11.92 ppm (s, 1H, NH, D_2O exchangeable); ^{13}C nmr (DMSO-d_6) δ 18.7, 25.3, 26.0, 30.2, 31.8, 32.1 ($6CH_2$), 117.4, 120.5, 128.6, 129.5, 130.0, 130.5, 131.4, 134.7, 144.7, 159.8, 162.8, 171.0 ppm (aromatic carbons & CN). *Anal.* Calcd. for $C_{20}H_{19}N_3S_2$ (365.38): C, 65.74; H, 5.24; N, 11.50. Found: C, 65.64; H, 5.14; N, 11.68.

2-(4'-Oxo-2'-penten-2-yl)amino-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (14). A mixture of **2** (2.06 g, 10 mmoles) and acetylacetone (1.34 g, 10 mmoles) was fused at 130°C in oil bath for 10 minutes. The fused product was dissolved in anhydrous DMF (10 mL), then poured onto ice cold water. The solid product, so formed, was collected by filtration and recrystallized from a mixture of *Et*OH/DMF (2:1) as brown solid; 2.37 (78%), mp. 96-98°C; ir: ν 3428-3218 (NH), 2924, 2847 (CH_2), 2195 (CN), 1619 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.34-1.52 (m, 8H, 5-, 6-, 7-, and 8-H), 1.53 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.46-2.16 (m, 4H, 4-, and 9-H), 6.90 (s, 1H, 3'-H), 7.95 ppm (br.s, 1H, NH); ms: *m/z* 288 (M^+). *Anal.* Calcd. for $C_{16}H_{20}N_2OS$ (288.36): C, 66.44; H, 6.99; N, 9.71. Found: C, 66.53; H, 6.92; N, 9.75.

2-Acetamido-4,5,6,7,8,9-hexahydrocycloocta[*b*]thiophene-3-carbonitrile (17). A solution of **2** (2.06 g, 10 mmoles) in acetic acid(20 mL) was treated with cyclohexanone (0.98 g, 10 mmoles). The reaction was refluxed for 10 hours and poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallized from *Et*OH as brown crystal, 1.68 g (68%), mp. 101-102°C; ir: ν 3263-3215 (NH), 2924, 2849 (CH_2), 2219 (CN), 1691 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31-1.54 (m, 8H, 5-, 6-, 7-, and 8-H), 2.17 (s, 3H, CH_3), 2.61-2.64 (t, 2H, CH_2, *J*=5 Hz), 2.69-2.72 (t, 2H, CH_2, *J*=5 Hz), 11.52 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 23.0, 25.9, 26.06, 27.3, 30.2, 31.2, 32.2 ($6CH_2$ & CH_3), 115.3 (CN), 120.3, 130.6, 134.7, 147.4 (thiophene carbons), 169.31 ppm (CO). *Anal.* Calcd. for $C_{13}H_{16}N_2OS$ (248.27): C, 62.89; H, 6.50; N, 11.28. Found: C, 63.05; H, 6.32; N, 11.25.

2-Amino-4-phenylhydrazo-4*H*-5,6,7,8,9-pentahydrocycloocta[*b*]thiophene-3-carbonitrile (19). To a cold solution 0 °C of **2** (2.05 g, 10 mmoles) in a mixture of *EtOH* (20 mL) and DMF (10 mL) containing NaOH (0.50 g), benzenediazonium chloride (1.28 g, 10 mmoles) was added with continuous stirring. The reaction mixture was stirred at room temperature for 2 hours. The solid product, so formed, was collected by filtration and recrystallized from a mixture of *Et*OH/DMF (2:1) as brown crystal, 1.80 g (64%), mp. 103-105°C; ir: ν 3443-3168 (NH_2 & NH), 2916, 2850 (CH_2), 2210 (CN), 1649

(C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.33-1.61 (m, 6H, 6-, 7-, and 8-H), 2.47-2.56 (m, 2H, CH_2), 2.64-2.76 (m, 2H, CH_2), 7.31-7.39 (m, 5H, phenyl protons), 8.86 (br.s, 2H, NH_2, D_2O exchangeable), 11.91 ppm (br.s, 1H, NH, D_2O exchangeable). *Anal.* Calcd. for $C_{17}H_{18}N_4S$ (310.35): C, 65.79; H, 5.85; N, 18.05. Found: C, 65.80; H, 5.87; N, 18.29.

Dimethyl-2-amino-11-cyano-10-phenylhydrazo-10*H*-5,6,7,8,9-pentahydrocycloocta[*c*]thiepine-3,4-dicarboxylate (23). A mixture of **19** (3.11 g, 10 mmoles) in dioxan (25 mL) containing acetic acid (2 mL)and DMAD (1.23 g, 10 mmoles) was refluxed for 5 hours. The reaction mixture was evaporated under *vacuo* and recrystallized from a mixture of DMF/*Et*OH (2:1) as brown crystal, 32.5 g (72%), mp. 103-105°C, ir: ν 3429-3217 (NH_2 & NH), 2924, 2850 (CH_2), 2200 (CN), 1735 (2CO ester), 1618(C=N) cm^{-1}, ^1H nmr (DMSO-d_6): δ 1.34-1.57 (m, 6H, 6-, 7-, and 8-H), 2.46-2.67 (m, 4H, 5-, and 9-H), 3.67 (s, 3H, OCH_3), 3.71 (s, OCH_3), 7.31-7.39 (m, 5H, phenyl protons), 9.84 (br.s, 1H, NH, D_2O exchangeable), 11.9 ppm (br.s, 2H, NH_2, D_2O exchangeable). *Anal.* Calcd. for $C_{23}H_{24}N_4O_4S$ (452.45): C, 61.05; H, 5.35; N, 12.38. Found: C, 61.13; H, 5.35; N, 12.38.

General Procedure for the Preparation of 25a-d. A mixture of either **1a** or **1b** (10 mmoles) and each of **24a** or **24b** (10 mmoles) was fused at 130-140°C for 5 minutes. The fused product was dissolved in Et*OH* (10 mL) and refluxed for 1 hour. The solid product, so formed, was collected by filtration and recrystallized from Et*OH*.

***N*-(2'-Benzotriazol-1-yl-1'-oxoethyl)-1*H*-cyclohexanone hydrazone (25a).** This compound was obtained as yellow crystals, 1.97 g (73%), mp. 150-152°C; ir: ν 3226-3112 (NH), 2924, 2853 (CH_2), 1693 (CO), 1649 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.51-1.66 (m, 6H, 3-, 4-, and 5-H), 2.24-2.31 (m, 4H, 2-, and 6-H), 5.88 (s, 2H, CH_2-Bt), 7.38-8.06 (m, 4H, benzotriazolyl protons), 10.9 ppm (br..s, 1H, NH, D_2O exchangeable), ms: *m/z* 271 (M^+). *Anal.* Calcd. for $C_{14}H_{17}N_5O$ (271.32): C, 61.97; H, 6.32; N, 25.82. Found: C, 61.88; H, 6.22; N, 25.72.

***N*-(2'-Benzotriazol-1-yl-1'-oxoethyl)-1*H*-cyclooctanone hydrazone (25b).** This compound was obtained as yellow crystals, 2.13 g (75%), mp. 201-202°C; ir: ν 3339-3187 (NH), 2925, 2859 (CH_2), 1682 (CO), 1634 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.38-1.75 (m, 10H, 3-, 4-, 5-, 6- and 7-H), 2.31-2.45 (m, 4H, 2-, and 8-H), 5.87 (s, 2H, CH_2-Bt), 7.39-8.04 (m, 4H, benzotriazolyl protons), 10.72 ppm (br.s, 1H, NH); 13C nmr (DMSO-d_6): δ 25.7, 27.7, 28.2, 36.9 ($4CH_2$), 49.9 (CH_2-Bt), 111.9, 119.9, 124.7, 128.2, 134.9, 146.0 (benzotriazolyl carbons), 161.3 (C-1), 168.3 ppm (CO). *Anal.* Calcd. for $C_{16}H_{21}N_5O$ (299.37): C, 64.19; H, 7.07; N, 23.39. Found: C, 64.29; H, 7.01; N, 23.27.

***N*-(2'-Cyano-1'-oxoethyl)-1*H*-cyclohexanone hydrazone (25c).** This compound was obtained as yellow crystals, 2.54 g (75%), mp. 230-232°C; ir: ν 3339-3223 (NH), 2932, 2858 (CH_2), 2196 (CN), 1689 (CO), 1645 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.09-1.50 (m, 6H, 3-, 4-, and 5-H), 2.22-2.30 (m, 4H, 2- and 6-H), 4.02 (s, 2H, CH_2CN), 10.52 ppm (br.s, 1H, NH, D_2O exchangeable). *Anal.* Calcd. for $C_9H_{13}N_3O$ (179.22): C, 60.31; H, 7.31; N, 23.44. Found: C, 60.21; H, 7.23; N, 23.34.

***N*-(2'-Cyano-1'-oxoethyl)-1*H*-cyclooctanone hydrazone (25d).** This compound was obtained as yellow crystals, 1.26 g (61%), mp. 242-243°C; ir: ν 3200 (NH), 2932, 2857 (CH_2), 2256 (CN), 1665 (CO), 1633 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.34-1.71 (m, 10H, 3-, 4-, 5-, 6- and 7-H), 2.25-2.41 (m, 4H, 2-, and 8-H), 4.00 (s, 2H, CH_2CN), 10.63 ppm (br.s, 1H, NH, D_2O exchangeable). *Anal.* Calcd. for $C_{11}H_{17}N_3O$ (207.27): C, 63.74; H, 8.27; N, 20.27. Found: C, 63.94; H, 8.26; N, 20.22.

General Procedure for the Preparation of 26a-d. A solution of each **24b** or **24d** (10 mmoles) and DMF DMA (1.33 g, 10 mmoles) in xylene (20 mL) was refluxed for 6 hours. The reaction mixture was cool at room temperature. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from EtOH.

***N*-(2'-Benzotriazol-1-yl-1'-oxoethyl)-2,8-dimethylamino-methylidenyl-2,8-dihydro-1*H*-cyclooctanone hydrazone (26a).** This compound was obtained as yellow crystal; 2.94 g (72%), mp. 161-1620C; ir: ν 3412, 3215 (NH), 2977, 2853 (CH_2), 1684 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.27-1.66 (m, 2H, 5-H), 1.73-1.86 (m, 4H, 4- and 6-H), 2.41-2.54 (m, 4H, 3- and 7-H), 2.76 (s, 6H, $N(CH_3)_2$); 2.96 (s, 6H, $N(CH_3)_2$); 5.80 (s, 2H, CH_2-Bt), 7.34-7.52 (m, 4H, benzotriazolyl protons), 7.85 (s, 2H, ylidene protons), 8.83 ppm (br.s, 1H, NH), ms: *m/z* 409 (M^+). *Anal.* Calcd. for $C_{22}H_{31}N_7O$ (409.51): C, 64.60; H, 7.56; N, 23.96. Found: C, 64.51; H, 7.50; N, 23.76.

***N*-(2'-cyano-1'-oxoethyl)-2,8-dimethylaminomethylidenyl-2,8-dihydro-1*H*-cyclooctanone hydrazone hydrochloride (26b).** This compound was obtained as yellow crystal; 2.15 g (61%), mp. 102-104°C, ir: ν 3381 (NH), 2924, 2855 (CH_2), 2180 (CN), 1693 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.35-1.47 (m, 2H, 5-H), 1.68-1.71 (m, 4H, 4- and 6-H), 2.31-2.83 (m, 4H, 3- and 7-H), 2.77 (s, 6H, $N(CH_3)_2$), 2.95 (s, 6H, $N(CH_3)_2$), 4.00 (s, 2H, CH_2CN), 7.75 (s, 2H, ylidene protons), 9.10 ppm (br.s, sH, NH); ms: *m/z* 317 (M^+-HCl). *Anal.* Calcd. for $C_{17}H_{28}ClN_5O$ (353.83): C, 57.70; H, 7.97; N, 19.79. Found: C, 57.72; H, 7.82; N, 19.69.

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 medium for bacterial test and Sabourand agar for fungal test. After placing the same volume in wells of all tested microorganism, nutrient agar plates were incubated at 37 °C for 24 hours and Sabourand dextrose agar plates were incubated at 25 °C for 48 hours. The diameter of zones inhibition was measured in millimeters and the results are shown in Table 1. 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 references.

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