Synthesis and Antimicrobial Activity of Novel Furothienoquinoxalines, Pyranothienoquinoxalines and Pyrimidopyranothienoquinoxalines

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The reaction of ethyl-3-mercaptoquinoxaline-2-carboxylate with phenacyl bromide, ethyl chloroacetate, chloroacetonitrile or chloroacetone furnished the corresponding 3-hydroxy thieno[2,3-*b*]quinoxaline. 2-Cyano-3-hydroxythieno[2,3-*b*]quinoxaline and 2-acetyl-3-hydroxythieno[2,3-*b*]quinoxaline were employed as precursors in the synthesis of some novel furo[2′,3′:4,5]thieno[2,3-*b*]quinoxaline, pyrano-[2′,3′:4,5]thieno[2,3-*b*]quinoxaline and other heterocyclic systems fused with thieno[2,3-*b*]quinoxalines. The antibacterial and antifungal activities of some the synthesised compounds were studied.

INTRODUCTION

Earlier we have reported the synthesis and reactions of some new quinoxaline derivatives in view of the significant biological activites of the compounds having quinoxaline nucleus.[1,2] For example, the 1,2,3,4-tetrahydroquinoxaline ring system is an important structural unit in many bioactive compounds:[3] 1,4-dihydro-6,7-dimethylquinoxaline-2,3-diones as Flavin metabolites and AMBA antagonists,[4] N-aryl-5-aminomethylquinoxaline-2,3-diones as both NMDA/glycin and AMDA receptor antagonists,[5] for anticancer efforts, and cytotoxics.[6] 1*H*-imidazo-[4,5-*g*]quinoxaline-4,9-diones and other some quinoxaline derivatives were used as antivirus (Hepatits B),[7] also, some quinoxaline derivatives are used as antibiotics,[8] antiherpes,[9,10] and antituberculotics.[11] Some quinoxaline derivatives with retinoic acid receptors and agonistic activity have been similarly evaluated.[12] In this respect and also for continuation of our earlier work for the synthesis of many fused heterocyclic systems containing quinoxalinemoiety,[13-17] we were concerned with the use of ethyl-3-mercapto-quinoxaline-2-carboxylate[15] for the synthesis of many fused quinoxaline heterocycles of a new type and it therefore was tested against bacteria and fungi.

RESULTS AND DISCUSSION

The thiation of ethyl(quinoxalin-2(1*H*)-one)-3-carboxylate **1** using P_2S_5 in dry pyridine resulted in the formation of thioxo derivative **2**; the latter compound was reported by another method[15] which was used as a potential starting material for the synthesis of the target heterocycles. Thus, the reaction of **2** with halocompounds like ω-bromoacetophenone and/or ethyl chloroacetate in the presence of fused sodium acetate gave the thienoquinoxaline derivatives **3** and **4**, respectively. Compound **4** was refluxed in an ethanolic solution of sodium hydroxide which resulted in hydrolysis followed by spontaneous decarboxylation to give 3-hydroxy-thieno[2,3-*b*]quinoxaline **6**. The cycloaddition reaction of **6** with benzylidenemalononitrile afforded 2-amino-3-cyano-4-phenyl-4*H*-pyrano[2′,3′:4,5]thieno[2,3-*b*]quinoxaline **7** in good yield. The condensation of *o*-aminonitrile **7** with triethyl orthoformate yielded methanimidate **8**, while the heating of **7** with acetic anhydride at reflux temperature led to the formation of monoacetyl derivative **9** (Scheme I).

The present invistigation was extended to the synthesis of novel furo[2′,3′:4,5]thieno[2,3-*b*]quinoxalines. The reaction of **2** with chloroacetonitrile in refluxing ethanol containing fused sodium acetate gave 2-cyano-3-hydroxythieno-[2,3-*b*]quinoxaline **10** which was reacted with ethyl chloroacetate in DMF at 100 °C for 3 hr in the presence of K_2CO_3 to give ethyl-(2-cyano-thieno[2,3-*b*]quinoxalin-3-yloxy)acetate **11**. Upon treatment with sodium ethoxide in refluxing ethanol.**11** underwent Thorpe-Ziegler cyclyization to furnish ethyl-(3-aminofuro[2′,3′:4,5]thieno[2,3-*b*]quinoxaline)-2-carboxylate **12**. Heating of **12** with formamide resulted in the formation of the pyrimidofurothienoquinoxaline derivative **13**. Reaction of *o*-hydroxycyano compound **10** with chloroacetonitrile under the same conditions afforded 3-amino-2-cyanofuro[2′,3′:4,5]thieno[2,3-*b*]quinoxaline **14**, which was cyclized to 4-amino-pyrimidofurothieno quinoxaline **15** (Scheme II).

2-Acetyl-3-hydroxythieno[2,3-*b*]quinoxaline **16** was produced from the reaction of **2** with chloroacetone. This

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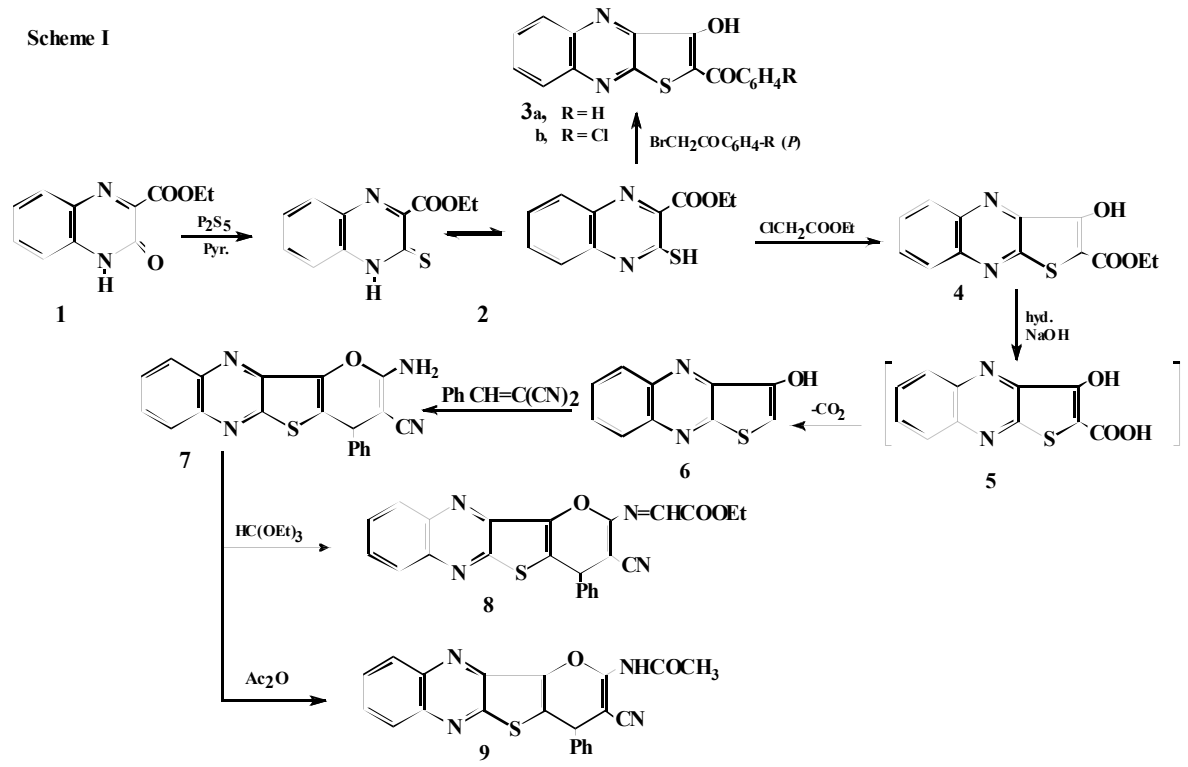
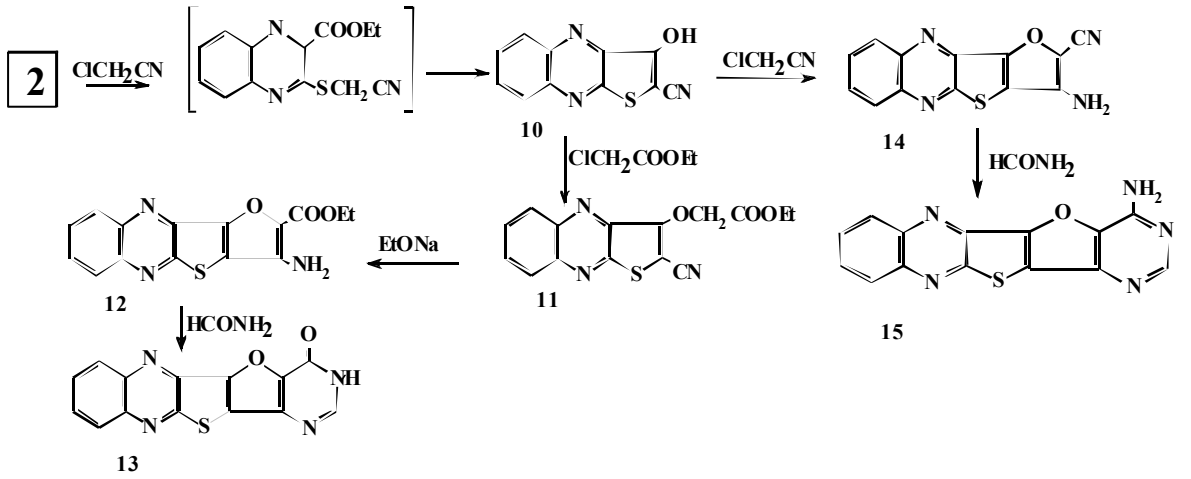
Scheme I



Scheme II

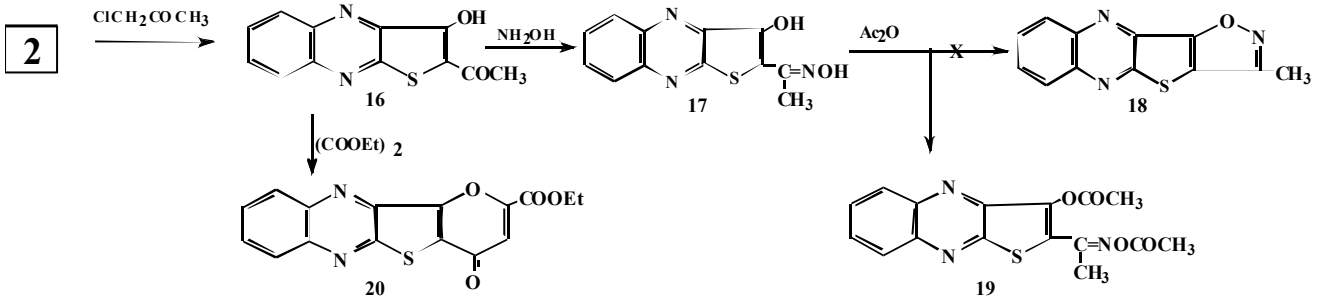


proved also to be a ver sa tile synthon for the preperation of other new thienoquinoxalines; thus, its con den sa tion with hydroxylamine gave the cor re spond ing oxime **17**. An at tempt to cyclize **17** to the isoxazolothienoquinoxaline **18** by heat ing with ace tic an hy dride failed, and the biacetyl de riv a tive **19** was iso lated in stead. Ring clo sure of **16** through re ac tion with di ethyl ox a late gave ethyl-(3-*H*-pyrano[2′,3′:4,5]thieno [2,3-*b*]quinoxalin-4-one)-2-carboxylate **20** (Scheme III).

Screening for Antimicrobial Activities

Most syn the sized com pounds (**2**, **3a**, **6**, **8**, **10**, **11**, **12**, **14** and **20**) were tested for their antimicrobial ac tiv i ties in vi tro against three strains of bac te ria: Gram postive *Ba cil lus subtillus*, *Micrococcus luteus* and Gram neg a tive *Ser ra tion rhodenil*

Scheme III



and three species of fungi: *Aspergillus fumigatus, Penicllum chrysogen*, and *Fusarium equiseti* using the filter paper technique[18,19] by measuring the zone of inhibition in mm at 25μg concentration. The screening results given in Table 1 indicated that among the tested compounds, **3a**, **6**, **8**, **10**, **12**, **14** and **20** showed good growth inhibition against Gram postive bacteria, but only two compounds, **6** and **14**, showed good growth inhibition against Gram negative bacteria. However, concerning the antifungal activities, only compound **6** was active against all types of fungi that were used but compound **11** was active against *Fusarium equiseti* only (Table 1).

EXPERIMENTAL

Melting points were determined on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using KBr wafer technique. ^1H NMR spectra were measured on a Varian 390-90 MHz NMR spectrometer in a suitable deutreated solvent, using TMS as the internal standard. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer. Elemental analysis gave acceptable results unless otherwise stated. Melting Points, Yields and Spectroscopic data are listed in Tables 2 and 3.

Ethyl(3-mercaptoquinoxaline)-2-carboxylate (2)

Compound **2** was prepared according to the literature,[15] m.p. 210 °C.

3-Hydroxy-2-benzoylthieno[2,3-*b*]quinoxaline (3a)
3-Hydroxy-2-*p*-chlorobenzoylthieno[2,3-*b*]quinoxaline (3b)
Ethyl(3-hydroxythieno[2,3-*b*]quinoxaline)-2-carboxylate (4)

General Procedure

A mixture of **2** (0.01 mol), fused sodium acetate (0.02 mol), and halocompounds (0.01 mol) in abs. ethanol (20 mL) was heated under reflux for 3 hr. The reaction mixture was diluted with (50 mL) H_2O. The solid precipitate was collected and recrystallized from the proper solvent.

3a was obtained by reaction of **2** with phenacyl bromide.

Table 1. Antimicrobial Activities of the Select Compounds [zone of inhibiton in mm]

Comp. No.	Antibacterial activity			Antifungal activity		
	Bacillus subtillus	*Micrococcus luteus*	*Serration rhodenil*	*Aspergillus fumigatus*	*Penicllum chrysogen*	*Fusarium equiseti*
2	-	-	-	-	-	-
3a	9	24	-	-	-	-
6	14	14	9	18	17	11
8	8	-	-	-	-	-
10	8	-	-	-	-	-
11	-	-	-	8	-	-
12	8	20	-	-	-	-
14	12	-	9	-	-	-
20	9	19	-	-	-	-

Table 2. Physical Data of Compounds **3-20**

Comp. No.	M.P. °C	Yield%	Formula Mol.Wt
3a	300	75	$C_{17}H_{10}N_2O_2S$ 306
3b	285	71	$C_{17}H_9N_2O_2SCl$ 340.5
4	198-200	75	$C_{13}H_{10}N_2O_3S$ 274
6	223	65	$C_{10}H_6N_2OS$ 202
7	288	70	$C_{20}H_{12}N_4OS$ 356
8	256-57	77	$C_{24}H_{16}N_4O_3S$ 440
9	>300	70	$C_{22}H_{14}N_4O_2S$ 398
11	112	80	$C_{15}H_{11}N_3O_3S$ 313
12	224	90	$C_{15}H_{11}N_3O_3S$ 313
13	>360	80	$C_{14}H_6N_4O_2S$ 294
14	290	72	$C_{13}H_6N_4OS$ 266
15	>360	75	$C_{14}H_7N_5OS$ 293
16	245-46	90	$C_{12}H_8N_2O_2S$ 244
17	280	77	$C_{12}H_9N_3O_2S$ 259
19	240	73	$C_{16}H_{13}N_3O_4S$ 343
20	236-37	85	$C_{16}H_{10}N_2O_4S$ 326

3b was obtained by reaction of **2** with *p*-chlorophenacyl bromide.

4 was obtained by reaction of **2** with ethyl chloroacetate.

3-Hydroxy-(2*H*)-thieno[2,3-*b*]quinoxaline (6)

A solution of **4** (0.01 mol) in (30 mL) ethanolic sod.hydroxide 10% was heated under reflux for 3 hr; and left to cool. The reaction mixture was diluted with (40 mL) H_2O and acidified with dilute HCl. The solid obtained was filtered off and recrystallized from acetic acid as brown crystals.

2-Amino-3-cyano-4-phenyl-(4*H*)-pyrano[2′,3′:4,5]thieno-[2,3-*b*]quinoxaline (7)

To a mixture of **6** (0.01 mol) and benzylidene malononitrile in (20 mL) ethanol, a few drops of piperidine were added. The reaction mixture was heated under reflux for 3 hr. The solid which precipitated while hot was filtered off and recrystallized from ethanol as pale red crystals.

3-Cyano-4-phenyl-(4*H*)-pyrano[2′,3′:4,5]thieno[2,3-*b*]-quinoxaline-2-methaimidate (8)

A suspension of **7** (0.01 mol) in (15 mL) triethyl orthoformate was heated under reflux for 3 hr; and allowed to cool. The precipitated solid was filtered off and crystallized from ethanol as red crystals.

3-Cyano-2-acetylamino-4-phenyl-(4*H*)-pyrano[2′,3′:4,5]-thieno[2,3-*b*]quinoxaline (9)

A solution of **7** (0.02 mol) in acetic anhydride (35 mL) was refluxed for 3 hr; the reaction mixture was cooled, then diluted with water (10 mL). The solid formed was filtered off and recrystallized from ethanol as yellow crystals.

2-Cyano-3-hydroxythieno[2,3-*b*]quinoxaline (10)

A mixture of **2** (0.01 mol) and chloroacetonitrile (0.01 mol) sodium acetate (0.025 mol) in abs.ethanol (40 mL) was refluxed for 2 hr. The solid obtained upon dilution with water was filtered off and recrystallized from ethanol as red crystals.

Ethyl(2-cyano-thieno[2,3-*b*]quinoxalin-3-yloxy)acetate (11)

A mixture of **10** (0.01 mol) and ethyl chloroacetate (0.01 mol) sodium acetate (0.02 mol) in abs.ethanol (35 mL) was refluxed for 2 hr; then poured onto cold water. The solid obtained was filtered off and recrystallized from ethanol as brown crystals.

Ethyl(3-aminofuro[2′,3′:4,5]thieno[2,3-*b*]quinoxaline)-2-carboxylate (12)

A suspension of **11** (0.015 mol) in sodium ethoxide solution (1.0 g sodium in 100 mL abs.ethanol) was heated under reflux for 30 min. The solid product separating on cooling was collected and recrystallized from ethanol as deep red crystals.

2,3-Dihydropyrimido[4″,5″:4′,5′]furo[2′,3′:4,5]thieno[2,3-*b*]quinoxalin-4-one (13)

A solution of **12** (0.5 g) in formamide (15 mL) was heated under reflux for 4 hr. The precipitate separating after cooling was collected and recrystallized from acetic acid.

3-Amino-2-cyanofuro[2′,3′:4,5]thieno[2,3-*b*]quinoxaline (14)

The title compound was prepared by reaction of **10** with

Table 3. Spectral Data of Compounds **3-20**

Comp.	IR (ν cm^{-1}) / ^1H NMR δ (ppm)
3a	3450 (OH), 1710 (CO), 1610 (C=N); (DMSO-d_6): δ 7.3-7.8 (m, 9H, Ar-H), δ 12.7 (s, 1H, OH).
3b	3500 (OH), 1700 (CO), (DMSO-d_6): δ 7.3-7.8 (m, 9H, Ar-H, OH).
4	3530 (OH), 2900 (CH aliph.), 1720 (CO), 1620 (C=N); ($CDCl_3$): δ 1.1-1.4 (t, 3H, CH_3), δ 3.2-3.6 (q, 2H, CH_2), δ 7.3-8.0 (m, 4H, Ar-H). δ 11.1 (s, 1H, OH).
6	3550-3320 (br. OH), ($CDCl_3$): δ 7.5-8.0 (m, 4H, Ar-H), δ 9.1 (s, 1H, CH).
7	3450 (NH_2), 2220 (CN), 1620 (C=N); (DMSO-d_6): δ 6.1 (s, 2H, NH_2), δ 7.5-8.3 (m, 9H, Ar-H).
8	2970 (CH aliph.), 2220 (CN), 1695 (CO), 1610 (C=N); (DMSO-d_6): δ 1.2-1.5 (t, 3H, CH_3), δ 3.2-3.6 (q, 2H, CH_2), δ 5.4 (s, 1H, CH pyran), δ 7.5-7.8 (m, 9H, Ar-H), δ 6.7 (s, 1H, N=CH).
9	3180 (NH), 2220 (CN), 1660 (C=O); (DMSO-d_6): δ 2.4 (s, 3H, CH_3), δ 5.7 (s, 1H, CH pyran), δ 7.3-7.8 (m, 9H, Ar-H), 9.8 (s, 1H, NH).
11	2220 (CN), 1720 (C=O); (DMSO-d_6): δ 1.15-1.40 (t, 3H, CH_3), δ 3.2-3.5 (q, 2H, CH_2), δ 4.2 (s, 2H, CH_2), δ 7.4-8.1 (m, 4H, Ar-H).
12	3300 (NH_2), 1670 (CO); ($CDCl_3$): δ 1.2-1.5 (t, 3H, CH_3), δ 3.1-3.6 (q, 2H, CH_2), δ 5.8 (s, 2H, NH_2), δ 7.5-8.0 (m, 4H, Ar-H).
13	3220 (NH), 1680 (CO); (CF_3COOD): δ 7.5-8.2 (m, 4H, Ar-H), δ 9.3 (s, H, CH).
14	3320 (NH_2), 2220 (CN),1620 (C=N); (DMSO-d_6): δ 6.1 (s, 2H, NH_2), δ 7.6-8.1 (m, 4H, Ar-H).
15	3320 (NH_2), 1615 (C=N); (CF_3COOD): δ 7.5-8.15 (m, 4H, Ar-H), δ 9.5 (s, 1H, CH).
16	3550 (OH), 1700 (C=O), 1620 (C=N); ($CDCl_3$): δ 2.4 (s, 3H, CH_3), δ 7.2-7.8 (m, 5H, Ar-H and OH).
17	3580-3200 (br-OH), 1620 (C=N).
19	1760, 1700 (2C=O), 2990 (CH, aliph.); (CF_3COOD): δ 1.5 (s, 3H, CH_3), δ 2.5, 3.1 (2s, 6H, $2CH_3$), δ 7.5-8.10 (m, 4H, Ar-H).
20	2950 (CH, aliph.), 1720, 1680 (2C=O); ($CDCl_3$): δ 1.25-1.6 (t, 3H, CH_3), δ 3.1-3.4 (q, 2H, CH_2), δ 7.5-7.9 (m, 4H, Ar-H), δ 9.2 (s, 1H, CH).

chloroacetonitrile (0.01 mol) in (20 mL) DMF, potassium carbonate (0.02 mol), the reaction mixture was heated on a water bath for 2 hr, cooled, and diluted with water (20 mL). The precipitate was collected and recrystallized from acetic acid.

4-Amino-(2*H*)-pyrimido[4′,5′:4,5]furo[2′,3′:4,5]thieno[2,3-*b*]quinoxaline (15)

A solution of **14** (0.5 g) in formamide (15 mL) was heated under reflux for 5 hr. The precipitate separating on heating was collected and recrystallized from ethanol as yellowish crystals.

2-Acetyl-3-hydroxythieno[2,3-*b*]quinoxaline (16)

The title compound was prepared by reaction of **2** with chloroacetone (0.01 mol) in (20 mL) DMF, potassium carbonate (0.03 mol), the reaction mixture was heated on a water bath for 2 hr; cooled, and diluted with water (20 mL). The precipitate was collected and recrystallized from acetic acid as brownish crystals.

3-Acetyloxime-3-hydroxythieno[2,3-*b*]quinoxaline (17)

A mixture of **16** (0.005 mol), (0.005 mol) hyroxylamine hyrochloride and (0.005 mol) sodium acetate trihydrate in (30 mL) ethanol was heated under reflux for 5 hr. The solid formed after cooling was collected and recrystallized from ethanol as colourless crystals.

Synthesis of diacetyl derivative (19)

A solution of **17** (0.01 mol) in acetic anhydride (25 mL) was refluxed for 3 hr; then cooled and poured onto ice/water. The precipitate thus formed was collected and recrystallized from ethanol as pale yellow crystals.

Ethyl(pyrano[2′,3′:4,5]thieno[2,3-*b*]quinoxalin-(3*H*)-4-one)-2-carboxylate (20)

A mixture of *o*-acetyl compound **16** (0.01 mol) and diethyl oxalate (0.01 mol) in ethanol (20 mL) was refluxed for 3 hr; the solid product separated from the hot mixture was filtered off and recrystallized from ethanol as goldish yellow crystals.

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Key Words

Synthesis; Antimicrobial; Furothienoquinoxalines; Pyranothienoquinoxalines and pyrimidopyranothienoquinoxalines.

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