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SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF NEW DITHIENYL CONTAINING PYRAN, PYRANO[2,3-b] PYRIDINE, PYRANO[2,3-d]PYRIMIDINE AND PYRIDINE DERIVATIVES

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SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF NEW DITHIENYL CONTAINING PYRAN, PYRANO[2,3-b]PYRIDINE, PYRANO[2,3-d]PYRIMIDINE AND PYRIDINE DERIVATIVES

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Some new pyran **3,8**; pyrano[2,3-b]pyridine **4**; pyrano[2,3-d] pyrimidine **5,6,7** and **9**; pyridine **10-14** derivatives have been prepared. The structure of all the new compounds have been established on the basis of elemental analyses and spectroscopic data. All the synthesized compounds have been screened for their antibacterial activity. Pyranopyrimidinethione **7** and pyridinethione **10** exhibited a good antibacterial activity compared with the standard antibiotic Gentamycin.

Keywords: Pyran; pyranopyridine; pyranopyrimidines; pyridines and antibacterial activity

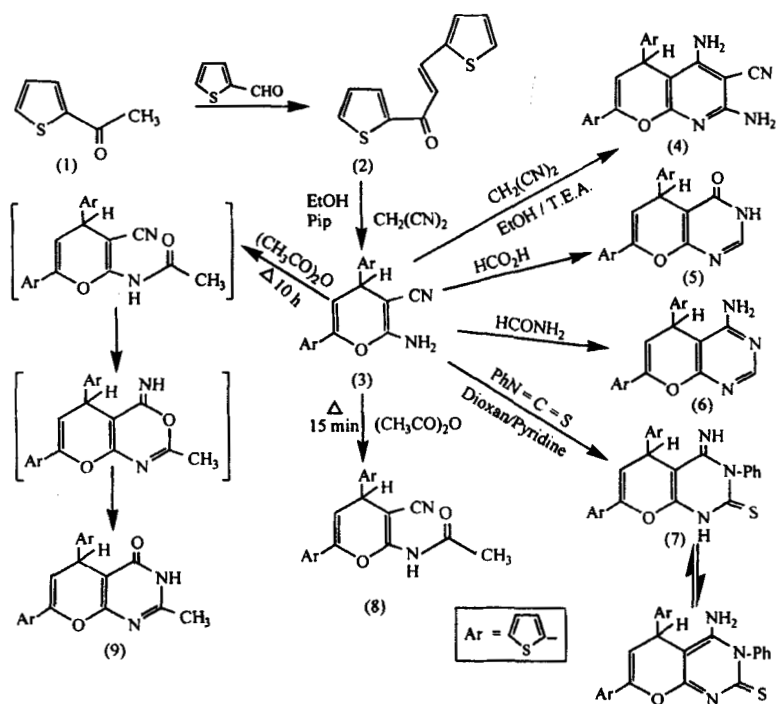
INTRODUCTION

Several polycyclic systems containing a fused pyran ring are reported to possess biological activity^[1-5]. Likewise, certain pyridines and pyranopyrimidines have been recently described to exhibit antimicrobial action^[6,7]. On the other hand, the antimicrobial activity has been found in several derivatives of thiophene^[8-10]. Based on these findings, and in continuation of our work on search for new antibacterial compounds^[11-14], we report here several new approaches to these derivatives.

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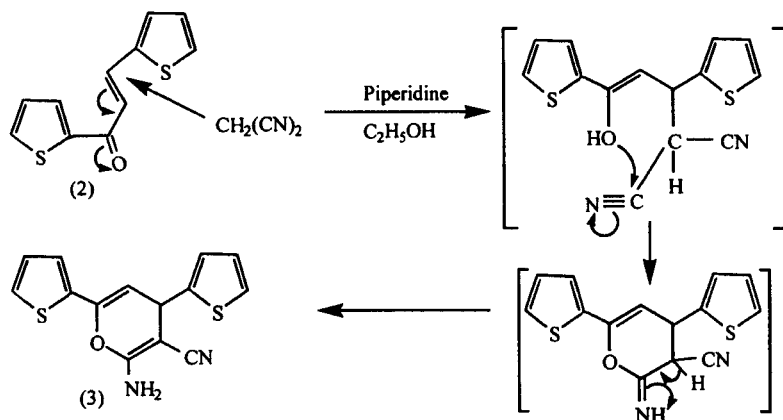
RESULTS AND DISCUSSION

Reaction of malononitrile with chalcone **2** in ethanol in the presence of piperidine afforded 2-amino-4,6-di(2-thienyl)-4*H*-pyran-3-carbonitrile **3** (Scheme 1), the structure **3** was established from elemental analysis and spectral data. Its IR spectrum showed an amino stretch at 3350, 3235 cm^{-1} , a cyano stretch of 2210 cm^{-1} and the 4*H*-pyran C=C bands at 1640 and 1610 cm^{-1} [15]. The ^1H -NMR spectrum of (**3** in DMSO- d_6) showed in addition to the aromatic signals, a broad singlet integrating for two protons at δ 5.9 which was attributed to the 2-amino group protons and two doublets at δ 4.7 ($J=2\text{Hz}$) and at δ 4.1 ($J=2\text{Hz}$) integrating for one proton each, which were assigned to H-4 and H-5 respectively; m/z 286 (M^+ , 10.65%), 272 (100), 243 (65.05); 220 (46.18), 191 (30.95), 111 (77.51), 84 (96.99), 69 (67.19).



SCHEME 1

The preparation of 2-amino-4*H*-pyran by Michael addition of ethyl cyanoacetate or malononitrile to *o*-benzoylcinnamonnitrile has also been reported^[16]. A proposed reaction mechanism for the formation of the 2-amino-4,6-di(2-thienyl)-4*H*-pyran-3-carbonitrile **3** is illustrated in (Scheme 2).



SCHEME 2

The present investigation represents the action of some active methylene compounds on **3**. Hence, condensation of **3** with malononitrile in refluxing ethanol in presence of triethylamine gave 5,7-diamino-6-cyano-2,4-di(2-thienyl)-4*H*-pyrano-[2,3-*b*]pyridine **4**. Structure **4** is supported by elemental analysis; IR spectrum, which showed bands at 3450, 3400, 3340, 3250 cm^{-1} (2NH_2), 2230 cm^{-1} ($\text{C}\equiv\text{N}$).

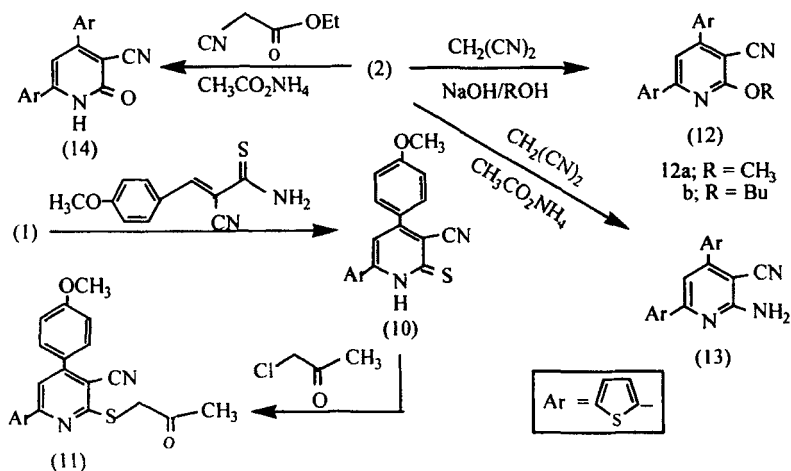
When **3** was refluxed with formic acid it afforded the corresponding 2,4-di(2-thienyl)-4,6-dihydro-5-oxo-pyrano[2,3-*d*]pyrimidine **5**, while with formamide the respective 5-amino-2,4-di(2-thienyl)-4*H*-pyrano[2,3-*d*]pyrimidine **6** was obtained (Scheme 1). The structure of **5** and **6** were determined from their correct elemental analysis and spectral data. IR of both **5** and **6** showed the absence of ($\text{C}\equiv\text{N}$), **5**: $\nu_{\text{max}}/\text{cm}^{-1}$ 3150 (NH), 1690 ($\text{C}=\text{O}$), 1630 ($\text{C}=\text{N}$); **6**: $\nu_{\text{max}}/\text{cm}^{-1}$ 3320, 3280, 1620 due to (NH_2), ($\text{C}=\text{N}$); m/z 313 (M^+ , 15.71%), 244 (29.34), 206 (15.99), 171 (13.90), 129 (27.69), 97 (59.59), 54 (100).

Interaction of **3** with phenyl isothiocyanate for a long time furnished 5-amino-2,4-di(2-thienyl)-4,6-dihydro-6-phenylpyrano[2,3-d]pyrimidin-7-thione **7**, $\nu_{\max}/\text{cm}^{-1}$ 3420 (NH), 1280 (C=S). δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 4.4 (1H, d, H-3 pyran), 4.7 (1H, d, H-4 pyran), 7.1–7.5 (11H, m, Ar-H + thienyl-H), 9.8 (2H, s, 2NH); m/z 421 (M^+ , 0.22%), 384 (0.28), 194 (86.43), 119 (8.74), 93 (100), 77 (45.82).

The reaction product of **3** with acetic anhydride varies with the time of reaction. When the reactants were refluxed for 15 min, 2-acetyl-amino-3-cyano-4,6-di (2-thienyl)-4H-pyran **8** was obtained (Scheme 1). $\nu_{\max}/\text{cm}^{-1}$ 3360 (NH), 2220 ($\text{C}\equiv\text{N}$), 1720 (C=O). δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 2.3 (3H, s, COCH_3), 4.5 (1H, d, H-5 pyran), 4.7 (1H, d, H-4 pyran), 7.2–7.6 (6H, m, thienyl-H), 10.1 (1H, s, NH). On the other hand 10 h reaction time afforded the 2,4-di(2-thienyl)-4,6-dihydro-5-oxo-7-methylpyrano[2,3-d]-pyrimidine **9**, $\nu_{\max}/\text{cm}^{-1}$ 3270 (NH), 1700 (C=O), δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 2.2 (3H, s, CH_3), 3.9 (1H, d, H-3 pyran), 4.3 (1H, d, H-4 pyran), 6.9–7.7 (6H, m, thienyl-H), 10.3 (1H, s, NH).

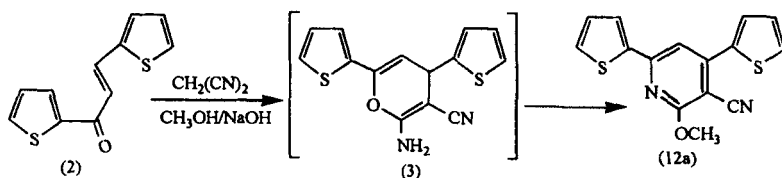
Condensation of 2-acetylthiophene **1** with p-methoxyphenylmethylene-cyanothioacetamide furnished 3-cyano-4(4'-methoxyphenyl)-6-(2thienyl)-2(1H)pyridinethione **10** (Scheme 3). $\nu_{\max}/\text{cm}^{-1}$ 3150 (NH), 2215 ($\text{C}\equiv\text{N}$), 1320 (C=S). δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 3.5 (3H, s, OCH_3), 7.0–7.6 (7H, m, Ar-H + thienyl-H), 8.3 (1H, s, CH pyridine), 9.2 (1H, s, NH); m/z 324 (M^+ , 41.97%), 293 (11.31), 213 (7.81), 185 (9.86), 129 (23.74), 97 (51.39), 54 (100). Treatment of **10** with chloroacetone yielded 2-acetyl-methylthio-4 (4'-methoxyphenyl)-6-(2-thienyl)-pyridine-3-carbonitrile **11**. $\nu_{\max}/\text{cm}^{-1}$ 2900 (CH aliphatic), 2210 ($\text{C}\equiv\text{N}$) 1680 (C=O) δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 2.5 (3H, s, COCH_3), 3.4 (3H, s, OCH_3), 3.9 (2H, s, SCH_2), 7.1–7.7 (7H, m, Ar-H + thienyl-H), 8.1 (1H, s, CH pyridine); m/z 380 (M^+ , 18.87%), 381 ($\text{M}+1$, 4.95), 324 (100), 293 (37.21), 229 (24.53), 163 (71.76), 90 (39.98), 82 (17.87).

The reaction of malononitrile with chalcone **2** in the presence of sodium hydroxide in methanol and/or n-butyl alcohol afforded 4,6-di-(2-thienyl)-2- methoxypyridine-3-carbonitrile **12a** and 2-butyloxy-4,6-di-(2-thienyl)-pyridine- 3-carbonitrile **12b**, respectively (Scheme 3). The IR spectra of the pyridines **12a,b** showed a nitrile stretch at 2220, 2200 cm^{-1} , and characteristic pyridine ring bands at 1610, 1595 and 1570, 1550 cm^{-1} [17]. δ_{H} of **12b** ($[\text{}^1\text{H}_6]$ DMSO) 1.9 (3H, t, CH_3), 3.5–4.2 (6H, m, $3\text{CH}_2\text{butyl}$), 7.2–7.6 (6H, m, thienyl-H), 8.3 (1H, s, CH pyridine).



SCHEME 3

A proposed route for the formation of the 2-methoxy-4,6-di-(2-thienyl)-pyridine-3-carbonitrile **12a** is shown in (Scheme 4), the initially formed 2-amino-4,6-di(2-thienyl)-4H-pyran **3** undergoes ring opening and subsequent pyridine ring formation, the pyridine nitrogen being driven from the 2-amino group.^[18–20]



SCHEME 4

Treatment of the chalcone **2** with malononitrile and/or ethyl cyanoacetate in presence of ammonium acetate in ethanol afforded 2-amino-4,6-di(2-thienyl)-pyridine-3-carbonitrile **13** and 2-oxo-4,6-di(2-thienyl)-pyridine-3-carbonitrile **14**, respectively (Scheme 3). **13**: $\nu_{\max}/\text{cm}^{-1}$ 3380, 3200 (NH_2), 2210 ($\text{C}\equiv\text{N}$), 1650 ($\text{C}=\text{N}$). **14**: $\nu_{\max}/\text{cm}^{-1}$ 3320 (NH), 2220 ($\text{C}\equiv\text{N}$), 1690 ($\text{C}=\text{O}$). **14**: δ_{H} ($[\text{}^1\text{H}_6]$ DMSO) 7.2–7.7 (6H, m, thienyl-H), 8.2 (1H, s, CH pyridine), 9.7 (1H, s, NH).

Biological Activity

The synthesized compounds (**3–14**), dissolved in dimethylformamide (DMF), were screened for their antibacterial activity against *Escherichia coli*, *Serratia marcescens*, *Staphylococcus aureus* and *Bacillus cereus*, using Gentamycin as a comparison standard antibiotic. The cup-diffusion technique was performed^[21].

The results (Table I) revealed that compound **7** containing thione and dithienyl moieties and compound **10** which contains methoxy, thione and thienyl moieties showed a promising activity equal to that of Gentamycin.

TABLE I Antibacterial activity of the synthesized compounds

Compd. ^a No.	Inhibition zone (mm)			
	<i>E. coli</i>	<i>S. marcescens</i>	<i>Staph. aureus</i>	<i>B. cereus</i>
3	16	-	14	15
4	14	12	12	12
5	12	10	-	16
6	-	12	18	10
7	27	26	28	24
8	10	-	15	13
9	-	16	12	-
10	30	28	30	24
11	18	12	-	-
12a	14	-	18	10
12b	-	12	20	-
13	-	10	15	10
14	16	14	-	-
DMF	-	-	-	-
Gentamycin ^b	28	27	30	25

a- in a concentration of 1 mg/ml DMF.

b- in a concentration of 0.2 mg/ml distilled H₂O.

On the other hand the other tested compounds showed a moderate antibacterial activities.

EXPERIMENTAL

Mps are uncorrected. Elemental analyses were carried out in the Micro-analytical Laboratories of the Faculty of Science, Cairo University. IR spectra (KBr discs) were measured on a Shimadzu IR 440 spectrophotometer. $^1\text{H-NMR}$ spectra were measured on a Varian GEMINI 200 instrument (200 MHz, $^1\text{H-NMR}$), using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were obtained using HP MODEL: MS-5988.

2-Acetylthiophene **1** and chalcone **2** were prepared according to a literature methods^[22,23].

2-Amino-4,6-di(2-thienyl)-4H-pyran-3-carbonitrile (3)

A mixture of chalcone **2** (0.01 mol) and malononitrile (0.01 mol) were dissolved in ethanol (30 ml), piperidine (8 ml) was added. The resulting solution was stirred at room temperature for 20 h, and then the solvent was evaporated. To the residue cold acetic acid solution (20 ml, 20%) was added and the precipitated product was filtered and crystallised from ethanol to give **3** (Table II).

5,7-Diamino-6-cyano-2,4-di(2-thienyl)-4H-pyrano[2,3-b]pyridine (4)

A suspension of **3** (0.01 mol) in ethanol (20 ml) containing a catalytic amount of triethylamine was treated with malononitrile (0.01 mol). The reaction mixture was refluxed for 10 h. The separated solid was filtered off and crystallised from ethanol to give **4** (Table II).

2, 4-Di(2-thienyl)-4,6-dihydro-5-oxo-pyrano[2,3-d]pyrimidine (5)

A solution of **3** (0.01 mol) in formic acid (20 ml) was refluxed for 6 h. The separated solid was collected and crystallised from ethanol-Benzene to give **5** (Table II).

5-Amino-2,4-di(2-thienyl)-4H-pyrano[2,3-d]pyrimidine (6)

A mixture of **3** (0.01 mol) in formamide (20 ml) was refluxed for 8 h. The solvent is removed under reduced pressure and the obtained solid was crystallised from DMF to give **6** (Table II).

TABLE II Characterization data of newly synthesized compounds 3–14

Compd. No.	M. P °C	Yield %	Mol.-formula	Analysis% Required / (Found)		
				C	H	N
3	248–50	86	C ₁₄ H ₁₀ N ₂ OS ₂	58.74 (58.50)	3.49 (3.20)	9.79 (9.40)
4	>360	81	C ₁₇ H ₁₂ N ₄ OS ₂	57.95 (58.20)	3.40 (3.70)	15.90 (15.60)
5	280–82	73	C ₁₅ N ₁₀ N ₂ O ₂ S ₂	57.32 (56.90)	3.18 (3.40)	8.91 (8.80)
6	>360	91	C ₁₅ H ₁₁ N ₃ OS ₂	57.50 (57.20)	3.51 (3.10)	13.41 (13.70)
7	140–42	63	C ₂₁ H ₁₅ N ₃ OS ₃	59.85 (59.50)	3.56 (3.20)	9.97 (9.70)
8	358–60	75	C ₁₆ H ₁₂ N ₂ O ₂ S ₂	58.53 (58.20)	3.65 (3.30)	8.53 (8.80)
9	200–202	69	C ₁₆ H ₁₂ N ₂ O ₂ S ₂	58.53 (58.20)	3.65 (3.80)	8.53 (8.70)
10	240–42	85	C ₁₇ H ₁₂ N ₂ OS ₂	62.96 (63.20)	3.70 (3.40)	8.64 (8.30)
11	>360	59	C ₂₀ H ₁₆ N ₂ O ₂ S ₂	63.15 (63.50)	4.21 (4.10)	7.36 (7.60)
12a	>360	64	C ₁₅ H ₁₀ N ₂ OS ₂	60.40 (60.60)	3.35 (3.10)	9.39 (9.20)
12b	>360	58	C ₁₈ H ₁₆ N ₂ OS ₂	63.52 (63.80)	4.70 (4.30)	8.23 (8.50)
13	120–22	78	C ₁₄ H ₉ N ₃ S ₂	59.36 (59.70)	3.18 (3.50)	14.84 (14.60)
14	350–52	72	C ₁₄ H ₈ N ₂ OS ₂	59.15 (58.80)	2.81 (2.50)	9.85 (9.50)

**5-Amino-2,4-di(2-thienyl)-4,6-dihydro-6-phenylpyrano
[2, 3-d]pyrimidine-7-thione (7)**

A mixture of **3** (0.01 mol), phenyl isothiocyanate (0.01 mol), dioxan (15 ml) and pyridine (2 ml) was heated under reflux for 24 h. The reaction mixture was then cooled poured into crushed ice. The resulting solid was washed with water, dried and crystallised from acetic acid to give **7** (Table II).

2-Acetylamino-3-cyano-4,6-di(2-thienyl)-4H-pyran (8)

A solution of **3** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 15 min to give N-acetyl derivative **8** (Table II).

2,4-Di(2-thienyl)-4,6-dihydro-5-oxo-7-methylpyrano[2,3-d]pyrimidine (9)

A solution of **3** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 10 h. The solid obtained was crystallised from acetic acid to give **9** (Table II).

3-Cyano-4(4'-methoxyphenyl)-6-(2-thienyl)-2 (1H)pyridinethione (10)

A mixture of **1** (0.01 mol), p-methoxyphenylmethylenecyanothioacetamide (0.01 mol) in ethanol (50 ml) containing ammonium acetate (1g) was refluxed for 5 h. The reaction mixture was cooled, filtered, washed with water, dried, and crystallised from ethanol to give **10** (Table II).

2-Acetylmethylthio-4(4'-methoxyphenyl)-6-(2-thienyl)-pyridine-3-carbonitrile (11)

Compound **10** (0.005 mol) was dissolved in ethanolic solution of sodium hydroxide (20 ml, 10%), then the chloroacetone (0.05 mol) was added and the mixture was heated under reflux for 15 minutes. After cooling, the reaction mixture was poured onto a cold water and the solid product formed was collected and crystallised from ethanol to give **11** (Table II).

General preparation for 2-alkoxy-4,6-di(2-thienyl)-pyridine-3-carbonitrile (12a,b)

The chalcone **2** (0.01 mol), and malononitrile (0.01 mol) were dissolved in the alcohol (methanol, *n*-butyl alcohol) (30 ml) and crushed sodium hydroxide pellets (2.0 g) were added. The mixture was stirred at room temperature for 18 h. The precipitated product was filtered off and crystallised from ethanol to give **12a,b** (Table II).

2-Amino-4,6-di(2-thienyl)-pyridine-3-carbonitrile (13)

A solution of the chalcone **2** (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (0.08 mol) in absolute ethanol (50 ml) was heated at reflux for 8 h. The reaction mixture was filtered while hot, concentrated under vacuum, and then left to cool in an ice-bath. The separated product was filtered and crystallised from ethanol to give **13** (Table II).

2-Oxo-4,6-di(2-thienyl)-pyridine-3-carbonitrile (14)

A solution of the chalcone **2** (0.01 mol), ethyl cyanoacetate (0.01 mol) and ammonium acetate (0.08 mol) in absolute ethanol (30 ml) was heated at reflux for 10 h and then cooled. The separated solid was filtered and crystallised from acetic acid to give **14** (Table II).

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