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SYNTHESIS OF SOME BENZOFURANYL THIENO[2,3-D] PYRIMIDINE DERIVATIVES WITH BIOLOGICAL INTEREST

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Abstract

Interaction of visnaginone or khellinone (**1a,b**) with cyanoacetamide, ethyl cyanoacetate or molanonitrile and elemental sulfur in presence of triethylamine afforded thiophene enamino derivatives (**2a-d**) respectively according to Gewald method. Acetylation of **2a** with acetic anhydride gave **3**. Condensation of **2b** with p-chlorobenzaldehyde yielded **4**. Compound **6** was afforded from reaction of enamino carboxamide (**2b**) with thiourea.. Compound **2b** reacted with benzoyl chloride to give thienopyrimidine (**8**). N-phenyl thienopyrimidine (**11**) and N-amino thienopyrimidine (**13**) were prepared from reaction of **2c** with phenyl isothiocyanate and hydrazinolysis of **12** with hydrazine hydrate.

The structures of these compounds were confirmed by infrared, mass and ¹H-NMR spectra. The biological activity of some compounds were discussed and found to be active.

Introduction

Many thienopyrimidine derivatives have been found to possess a wide span of medical activities including antihistaminic⁽¹⁾, antitumour⁽²⁾, antibrilatory⁽³⁾. Moreover, the rapid growth in the literature dealing with the synthesis and biological activity of thienopyrimidine derivatives prompted us to synthesis new derivatives of fused pyrimidine, thienopyrimidine derivatives.

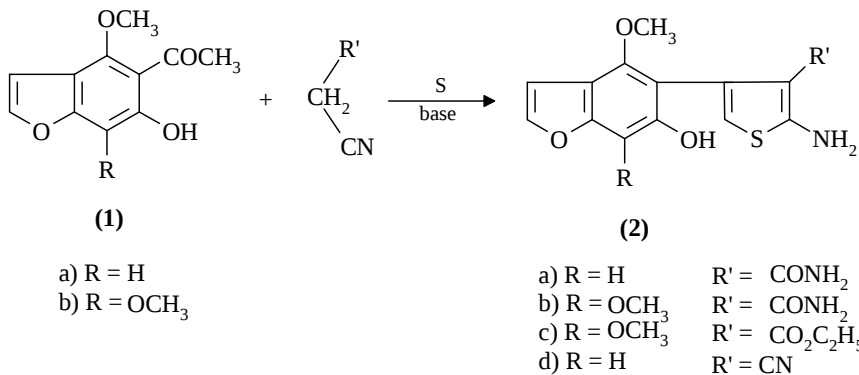
Besides some active compounds have been described when the thiophene moiety is fused to carbocyclic ring also, fused heterocyclic pyrimidine nucleosides have synthesized to exhibit prominent and versatile biological activities⁽⁴⁻¹³⁾.

On the other hand, thienopyridines possess remarkable activity against Herpes simplex virus type 1 (HSV-1)⁽¹⁴⁻¹⁸⁾.

Results and Discussion

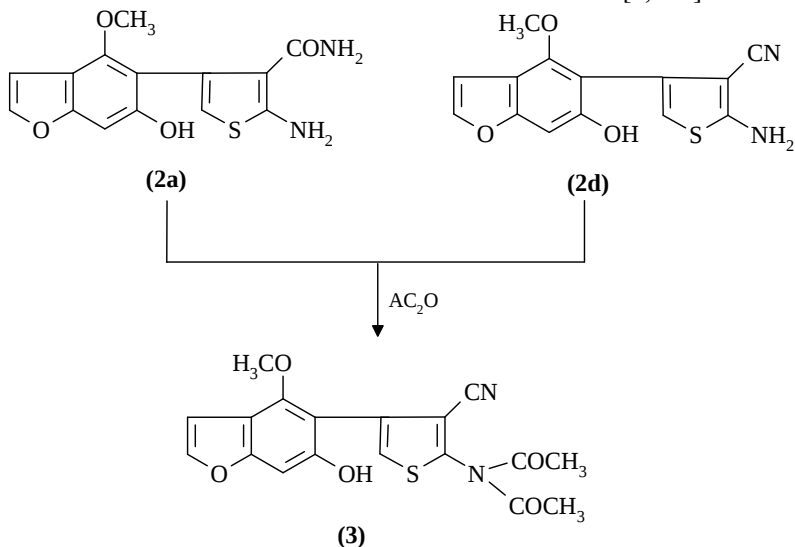
According to Gewald method⁽¹⁹⁾ thiophene enamino derivatives (**2a-d**) were obtained from the reaction of 5-[4-methoxy (4,7-dimethoxy)-6 hydroxy

benzofuranyl] methyl ketone (**1a,b**) with cyanoacetamide ethyl cyanoacetate or malononitrile and sulfur in presence of triethylamine.



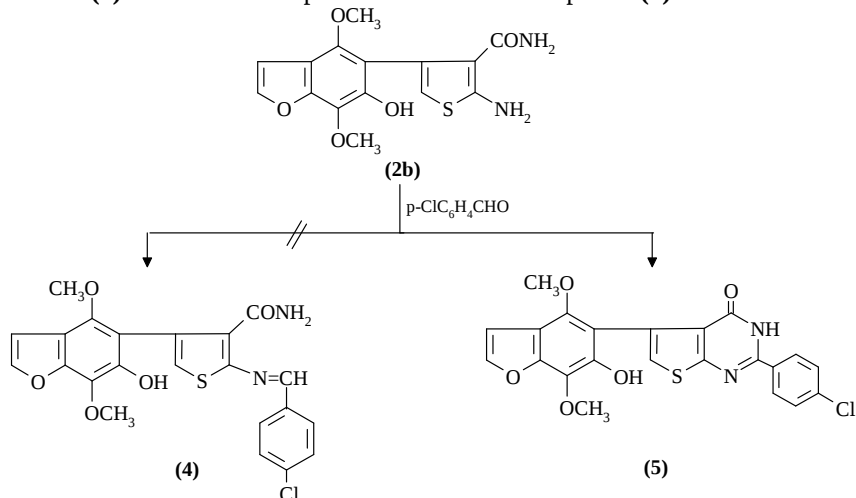
Compounds **2a-d** were confirmed by elemental analysis and spectroscopic evidences. Infrared spectra revealed to absorption bands for NH₂, (C≡N) and (C=O) groups as shown in Table (1).

Acetylation of enamino derivative (**2a**) with acetic anhydride consumed two moles of acetic anhydride followed by dehydrating the carboxamide group to afford 2-N,N-diacetyl thiophen 3-carbonitrile derivative (**3**). Also compound **3** was prepared from refluxing of thiophene enamino carbonitrile (**2d**) with acetic anhydride for 4hrs.

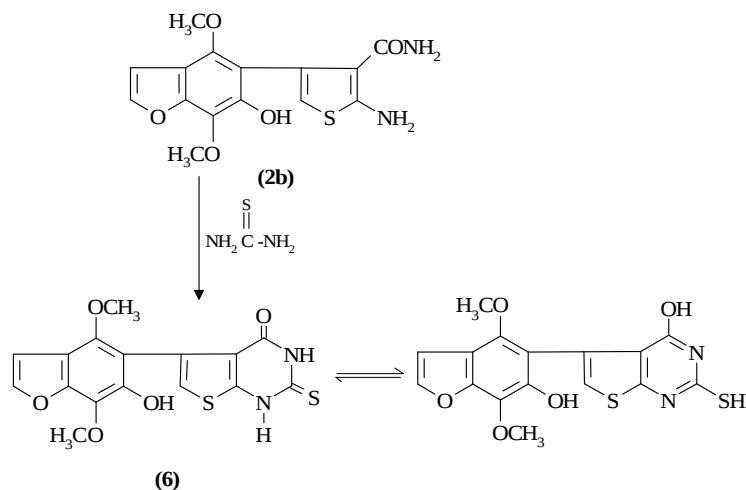


The structure of **3** was supported by correct elemental analysis and spectral data. Where IR spectrum showed absorption band at 2221 cm^{-1} characteristic for $(\text{C}\equiv\text{N})$ and gives colour with FeCl_3 , a similar acetylating has been reported previously⁽²⁰⁾.

Condensation of thiophene enamino carboxamide (**2b**) with *p*-chlorobenzaldehyde in ethanol, afforded the desired thieno [2,3-d] pyrimidine derivative (**5**) instead of the expected Schiff's base compound (**4**).

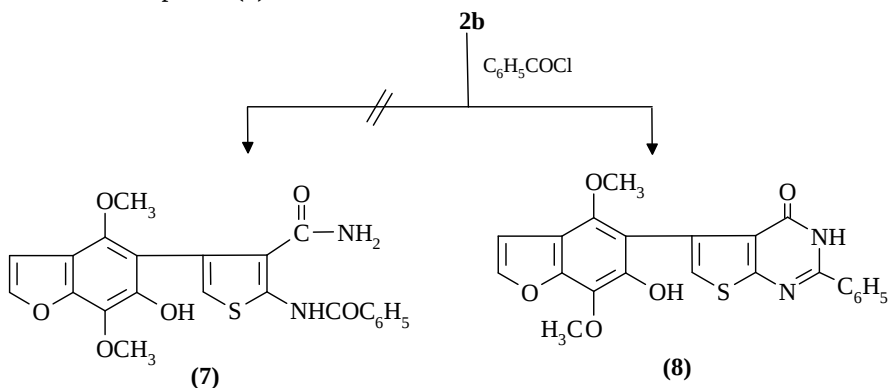


Treatment of **2b** with thiourea yielded 2-thioxo thieno [2,3-d] pyrimidine derivative (**6**).



The structure of **6** was assigned by spectroscopic and elemental data.

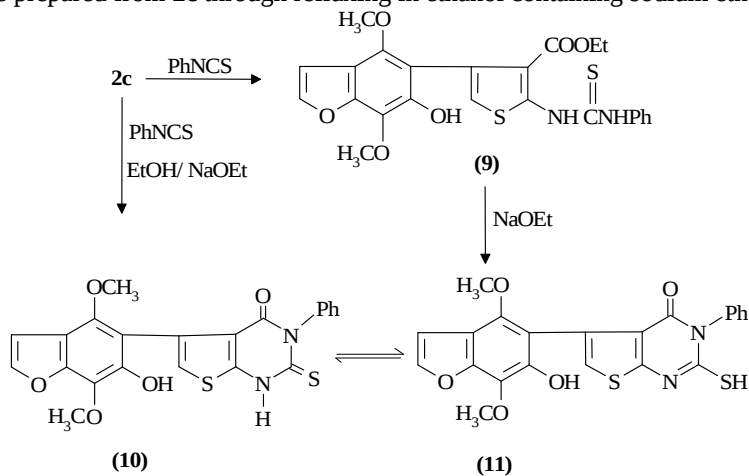
Also, interaction of the compound **2b** with benzoyl chloride affected cyclization to yield 2-phenyl thieno [2,3-d] pyrimidine derivative (**8**) instead of N-benzamide derivatives compound (**7**).



The structure of **8** was supported by spectral and elemental data.

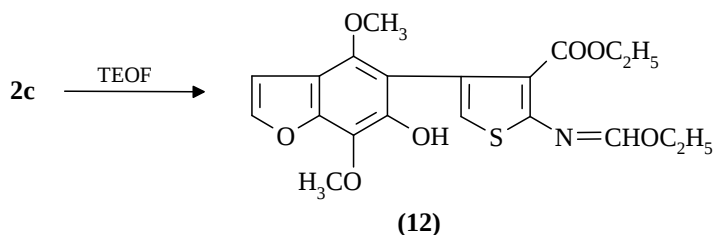
As an extension for the synthesis of the target compound (N-derivatives of thieno[2,3-d]-pyrimidine) the authors focused on incorporating ethyl 2-aminothiophen-3-carboxylate derivative (**2c**) with different reagents in the hope of obtaining compounds with different application. Thus compound **2c** reacted with phenyl isothiocyanate in ethanol to give thiourea derivative (**9**) which refluxed in ethanol in presence of sodium ethoxide which affected cyclization to produce the

desired derivative of N-phenyl thieno[2,3-d]pyrimidine (**11**). Also compounds **10** or **11** were prepared from **2c** through refluxing in ethanol containing sodium ethoxide.



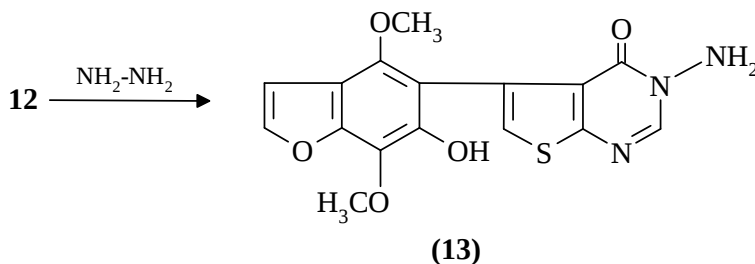
The assigned structures of **9**, **10** and **11** were in agreement with elemental analysis and spectral data. IR spectrum of **9** showed the presence of absorption band at 1773cm^{-1} ($\text{C}=\text{O}$) of ester and absence of this ($\text{C}=\text{O}$) in **10** or **11**.

When, ethyl 2-amino thiophen-3- carboxylate (**2c**) was refluxed with triethyl orthoformate gave **12**.



Structure of compound **12** was established from elemental analysis and spectral data. IR spectrum showed the disappearance of NH_2 group and $^1\text{HNMR}$ revealed signal 3.87 characteristic of ethyl group.

Hydrazinolysis of **12** with hydrazine hydrate in n-butanol affected cyclization to afford another desired N-amino thieno-[2,3-d] pyrimidine derivative (**13**).



The assigned structure of **13** was confirmed by spectroscopic and elemental data. IR spectrum of **13** revealed characteristic band at 3188 & 3126 of (NH₂).

Results of antimicrobial activity

The antimicrobial activity of some newly selected synthesized compounds was tested and the results are shown in (Table 3).

Among the compounds tested, it was noticed that compounds **4,5,6,11 and 13** showed significant antibacterial and antifungal activity.

Compounds **4,5,6, and 13** showed significant antibacterial and antifungal activity.

Compound **11** showed moderate activity against gram-negative *Escherichia coli*, gram-positive, *Bacillus subtilis*, yeast, *Syncephalastrum racemosum* and Fungi, *Pencillium italicum*

Experimental

Melting points were uncorrected and were determined on a Stuart melting point apparatus elemental analysis were determined on a perkin Elmer, 240 (micro analysis). Microanalytical laboratory Cairo University, Giza, Egypt. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (Shimadzu) Japan using KBr technique. ¹H-NMR spectra were recorded on a BRUKER proton NMR-Advance 300 (300MHz) in DMSO-d₆ as a solvent using (TMS) as internal standard and chemical shift (δ) in ppm. Mass spectra were run on HP MODEL MS-5988.

Synthesis of 2-Amino-5-[4-methoxy-(4,7-dimethoxy)-6-hydroxy benzofuran-5-yl]-3-carboxamide (2a,b) or and ethyl 2-amino-5-[4-methoxy-(4,7-dimethoxy)-6-

SYNTHESIS OF SOME BENZOFURANYL THIENO[2,3-D] 131

hydroxybenzofuranyl]-3-carboxylate (2_c) and 2-amino-5-[4-methoxy-6-hydroxy benzofuranyl]-3-carbonitrile.

A mixture of visnaginone (**1a**) or Khellinone (**1b**) (0.01 mol), cyano acetamide ethyl cyanoacetate or malononitrile (0.01 mol) and sulfur powder (0.01 mol) in ethanol (50 ml) containing, few drops of triethylamine was refluxed for 3hrs. The reaction mixture was cooled, the resulting solid was collected and crystallized from ethanol to give (**2_{a-d}**) Table (2).

The structure of **2a,b** were confirmed by elemental analysis and spectroscopic evidence.

Table (1)

Compound	$\nu_{\max./\text{cm}^{-1}}$
2a	3369(OH) , 3158 & 3135 (NH ₂) and 1622(C=O)
2b	3340 (OH/NH ₂) and 1616 (C=O)
2c	3334(OH/NH ₂) and 1686(C=O)
2d	3421(OH), 3150, 3123(NH ₂) and 2207 (C≡N).

Mass spectrum of **2a** exhibited a molecular ion peak at m/z 260 (M^+ -CONH₂, 3.92%) and other significant peak at 192 (20.6%), 160 (42.9%), 128 (53.7%) and a base peak at 64.

Mass spectrum of **2b** was in agreement with assigned structure, it revealed a molecular ion peak at [m/z 316, M^+ -H₂O (6.7%)] and other significant peaks at 313 (33%), 264 (18.2%), 236 (55.9%), 129(46.4%) and abase peak at 69.

The ¹H-NMR spectrum of (**2_c** in DMSO-d₆) showed signals at δ 1.79 (t, 3H, - ester), 3.90 (q, 2H, ester), 4.08 & 4.21 (2s, 6H, 2OCH₃), 4.77 (s, 2H, NH₂), 6.55 (s, 1H, thiophene) 7.22 (d, 1H, H₋₃ furan) ($J = 2.01$ Hz) 7.93 (d, 1H-H₋₂ furan moiety) ($J = 2.22$ Hz) and 11.59 (s, 1H, OH- exchangeable with D₂O).

The ¹H-NMR spectrum of compound **2_a** (CDCl₃): δ 3.82 & 3.95 ppm (2s, 6H, 2OCH₃), 4.83 (br. 2H, NH₂), 6.2 (s, 1H, thiophene.s moiety) 6.87 (d, 1H, H-3, furan moiety ($J = 2.01$ Hz), 7.49 (s, 1H, H-2 furan moiety) ($J = 2.22$ Hz) and 11.69 (s, 1H, OH-exchangeable with D₂O).

Synthesis 2-N,N-diacetyl-5-[4-methoxy-6-hydroxybenzofuran-5-yl]-3-carbonitrile (3).

A solution of (**2a**. 0.01 mol or **2d**) and acetic anhydride (20 ml) was refluxed for 6 hrs for **2b** and 4hrs for **2d**. The reaction mixture allowed to cool and poured in water, filtered, the resulting solid was collected and crystallized from ethanol to give **3**, Table (2).

The assigned structure of **3** was confirmed by correct elemental analysis and spectral data. Infrared spectrum showed absorption bands at 3341cm^{-1} (OH), 2221 ($\text{C}\equiv\text{N}$), 1771 and 1701 ($2\text{C}=\text{O}$).

Mass spectrum exhibited a molecular ion peak m/z at 368 [M^+-2H , (1.8%)] and the following fragments 278 (10.1%), (203 (20%) with a base peak 236.

Synthesis of 2-(p-chlorophenyl)-5-(4,7-dimethoxy-6-hydroxy Benzofuran-5-yl) thieno[2,3-d] pyrimidin-4(3H) one (5).

A solution of **2_b** (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) in ethanol (20 ml) was refluxed for 6hrs. the solvent was evaporated and the solid was obtained crystallized from petroleum ether (60-80) to give **5**, Table (2).

Structure **5** was supported by elemental analysis and spectral data. Infrared spectrum showed absorption bands at 3397 (OH), 3139 (NH), 1685 ($\text{C}=\text{O}$) and 1588 ($\text{C}=\text{N}$).

$^1\text{H-NMR}$ spectrum of **5** (CDCl_3) revealed signals at δ 3.96 & 4.08 (2s, 6H, 2OCH_3), 5.61(S, 1H, thiophene), 6.79 (d, 1H, H-3 furan moiety) ($J= 2.1\text{Hz}$), 6.87 – 7.35 (m, 5H, Ar + H_2 furan moiety), 7.48 (S, 1H, NH) and 12.07 (S, 1H, OH exchangeable with D_2O).

Synthesis of 2- Thioxo-5-(4,7-dimethoxy-6-hydroxy benzofuran-5-yl) thieno [2,3-d] pyrimidin-4(3H) one (6).

A mixture of **2_b** (0.01 mol) and thiourea (0.01 mol) in ethanol (10 ml) was refluxed for 3hrs. The reaction mixture was cooled, the resulting solid was collected and crystallized from ethanol to give **6**, Table (2).

The structure of (**6**) was supported with correct elemental analysis and spectral data. Infrared spectrum showed strong characteristic bands at 3377 cm^{-1} (OH), 3272, 3171(2NH) and 1613 ($\text{C}=\text{N}$).

Mass spectrum of **(6)** revealed a molecular ion peak m/z at 376 (19 %) and a base peak at 64 and other significant peaks at 359 (13%), 328(31%), 314 (7%).

Synthesis of 2-Phenyl-5-(4,7-dimethoxy-6-hydroxy benzofuran-5-yl) thieno [2,3-d] pyrimidin-4(3H)-one (8).

A mixture of **2_b** (0.01 mol) and benzoyl chloride (0.01 mol) was refluxed for 3hrs. The reaction mixture was cooled, the resulting solid was collected and crystaized from n-hexane to give **8** , Table (2).

The structure was confirmed from by elemental and spectral data. Infrared spectrum showed absorption bands at 3405 cm^{-1} [OH/NH], 1685 (C=O) and 1592 (C=N).

¹H-NMR spectrum [CDCl_3] revealed signals at δ 3.99 and 4.137 [2S, 6H, 2OCH₃], 6.47(S, 1H, thiophene), 7.01 (d, 1H, H-3 furan moiety) ($J = 2.21\text{ Hz}$) 7.3-7.97 (m, 6H, Ar + H₂ furan moiety), and 8.71 [S, 1H, NH]. Exchangeable with D₂O].

Synthesis of 3-carboxthoxy N-phenyl-N' [5-(4,7-dimethoxy-6-hydroxy benzofuran-5-yl) thiophen-2-yl] thiourea (9).

To a solution of **2c** (0.01 mol) in dry benzene (30 ml) phenyl isothiocynate (0.01 mol) was added and few drops of triethylamine. The reaction mixture was refluxed for 6hrs. The solvent was removed and the resulting solid was washed with methanol and recrystallized from n-hexane to give **9**, Table (2).

The assigned structures of **9**, was in agreement with elemental analysis and spectral data. Infrared spectrum of **9** appeared bands at 3276 [OH], 3195 & 3126 [NH] and 1773(C=O).

The mass spectrum of **9** exhibited a molecular ion peak at m/z 498 [M^+ , 0.22%] with a base peak at 236 and significant peaks at 220 (59.77%), 206 (24.81%), 128 (10.36%) and 55 (31.43%).

Synthesis of 2-Thioxo-3-phenyl-5-(4,7-dimethoxy-6-hydroxy benzofuran-5-yl) thieno [2,3-d]pyrimidine-4-one (10) or (11):

Compound **2c** or **9**, (0.01 mol) in sodium ethoxide (30 ml) was stirred at room temperature for 3hrs, the reaction mixture was cooled, and the resulting solid was filtered and crystallized from P.E. 60-80 to give **10 or 11**, Table (2).

Infrared spectrum of **10** showed the disappearance of carbonyl of ester group found in the parent compound and revealed bands at 3330(OH) 3135(NH) 1682 (C=O) and 1150 (C=S).

The mass spectrum of **10** afforded a molecular ion peak at m/z 452 [M^+ , 28.6%] with a base peak at 238 and the following peaks appeared at 136 (85.7%), 102 (84.8%) and 97 (57.1%).

Synthesis of 3-carboethoxy-5-(4,7-dimethoxy-6-hydroxy benzofuran-5-yl) thiophen-2-yl) imidoformate (12).

Compound **2c** (0.01 mol) was refluxed in a mixture of triethylorthoformate (10ml) and acetic anhydride (10 ml) for 3hrs. the solvent was removed under reduced pressure, and the remaining solid was recrystallized from dry dioxan to give **12**, Table (2). The structure of **12** was established from correct elemental analysis and spectral data.

Infrared spectrum of **12** revealed bands at 3423 (OH), 1682 (C=O) and 1552 (C=N). The ^1H NMR spectrum of compound **12** (DMSO- d_6) revealed signals at δ 1.25 & 1.92 (2t, 6H, 2CH₃ of 2CH₂CH₃). 3.87-4.122 [m, 10H, 2OCH₃ + 2CH₂ of C₂H₅], 6.52 (s, 1H, thiophene), 7.32 [d, 1H, H₋₃ furan moiety) ($J=2.2$ Hz 7.91 (d, 1H, H₋₂ furan moiety) ($J=2.12$ Hz) 8.2 (s, 1H, N=CH) and 11.54 (S, 1H, OH-exchangeable with D₂O)].

Synthesis of 3N-amino-5-[4,7-dimethoxy-6-hydroxy benzofuran-5-yl] thieno [2,3-d]pyrimidin-4-one(13).

To a solution of **12**, (0.01 mol) in n-butanol (20 ml) hydrazine hydrate (0.03 mol) was added. The reaction mixture was refluxed for 10 hrs. The resulting solid was filtered, crystallized from ethanol to give **13**, Table (2). The structure was assigned by elemental and spectral data. The infrared spectrum of **13** showed bands at 3443 (OH) & 3188 & 3126 [NH₂], 1677 (C=O) and 1558 (C=N).

The mass spectrum of **13** explained a molecular ion peak at m/z 359 [M^+ , 73.3%] with a base peak at 64 and the following peaks appeared at 256 (11.3%), 160 (19.0%) and 96 (17.0%).

Antimicrobial activity

Antimicrobial activity of some newly synthesized compounds **3,5,10,12** and **13** were tested in concentration of 0.1 g/ml using dimethyl formamide as a solvent against the same concentration of the reference standard; chloramphenicol which used as a standard antibacterial agent and terbinafin was used as a standard antifungal agent.

The test was done using the diffusion agar technique against all microorganism's species.

1) Bacteria

- a) Gram-positive bacteria, *Bacillus subtilis*, *Staphylococcus aureus*.
- b) Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa*

2) Yeast: *Candida albicans*, *Syncephalastrum racemosum*.

3) Fungi: *Aspergillus*, *Pencillium italicum*

Medium

The cap-assay method containing (g/l) peptone 6.0; yeast extract 3.0, meat extract 1.5, g, glucose 1.0 and 20g/l agar used. The medium was sterilized and divided while hot (50-60°C) in 15 ml. portions among sterile Petridishes of 8cm diameter. One ml of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petridish.

Method⁽²¹⁾

0.5 g from each of the tested compounds was dissolved in 5 ml of dimethyl formamide. An amount of 0.1 ml of test solution was placed on watman paper disc of 9 mm diameter and the solvent was left to evaporate. The saturated disc was placed carefully on the surface of the inoculated solid medium, each Petri-dish contains at least 3 discs. The Petri-dishes were incubated at 5°C for an hour to permit good diffusion and then transferred to an incubator of 85°C overnight then examined. The results were then recorded by measuring the inhibition zone diameters.

Table (2) :

Comp. No.	M.P. (°C)	Yield % color	Molecular formula	Analysis required/ found				Cl
				C	H	N	S	
2a	220	40	C ₁₄ H ₁₂ N ₂ O ₄ S (304.12)	55.29	3.97	9.21	10.54	
				55.31	4.01	9.01	10.66	

6	155	50	C ₁₅ H ₁₄ N ₂ O ₅ S (334.097)	53.92 54.10	4.22 4.32	8.38 8.41	9.59 9.68	
	2b							
	190	40	C ₁₇ H ₁₇ NO ₆ S (363.08)	56.24 56.42	4.72 4.81	3.86 3.90	8.88 8.91	
	122	40	C ₁₄ H ₁₀ N ₂ O ₃ S (286.31)	58.54 58.56	3.44 3.46	10.0 10.2	11.0 11.2	
4	65	50	C ₂₂ H ₁₅ N ₂ O ₅ SCl (454.63)	60.79 60.81	3.48 3.61	6.45 6.52	7.38 7.51	11.65 11.69
5	225	30	C ₁₈ H ₁₄ N ₂ O ₅ S (370.13)	58.41 58.33	3.81 4.01	7.57 7.71	8.66 8.81	
6	167	70	C ₁₆ H ₁₂ N ₂ O ₅ S ₂ (376.16)	51.088 51.11	3.22 3.31	7.45 7.54	17.049 17.10	
8	160	60	C ₂₂ H ₁₆ O ₅ N ₂ S (420.43)	62.88 62.90	3.84 3.90	6.67 6.69	7.63 7.55	
9	210	30	C ₂₄ H ₂₂ O ₆ N ₂ S ₂ (498.27)	57.85 58.01	4.45 4.61	5.62 5.72	12.87 13.01	
10	110	30	C ₂₂ H ₁₆ O ₅ N ₂ S ₂ (452.25)	58.43 58.34	3.57 3.67	6.19 6.21	14.18 14.20	
12	230	50	C ₂₀ H ₂₁ NO ₇ S (419.098)	57.32 57.33	5.05 5.22	3.131 3.13	7.65 7.71	
13	170	40	C ₁₆ H ₁₃ O ₅ N ₃ S (359.12)	53.51 53.54	3.65 3.72	11.7 11.91	8.93 9.01	

Table (3) Antimicrobial activity

Samples	4	5	6	11	13	St.
<i>Escherichia coli</i>	+	+	+	++	+	++
<i>Pseudomonas aeruginosa</i>	-	-	-	-	-	+++
<i>Staphylococcus aureus</i>	-	-	-	-	-	++
<i>Bacillus subtilis</i>	++	++	++	++	++	+++
<i>Candida albicans</i>	-	-	-	-	-	++
<i>Syncephalastrum racemosum</i>	+	+	+	++	+	+++
<i>Aspergillus fumigatus</i>	-	-	+	-	-	+++
<i>Penicilium italicum</i>	+	++	++	++	++	+++

St. reference chloramphenicol as a standard antibacterial agent

Terbinafin as a standard antifungal agent

+++ : Highly sensitive

++ : Fairly sensitive

+ : Slightly sensitive

- : No sensitive

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