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S. HESSEIN
Chemistry Department, Faculty of Science (Girl's), Al-Azhar University, Cairo, Egypt

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SYNTHESIS OF SOME NEW BENZOFURAN DERIVATIVES OF EXPECTED BIOLOGICAL ACTIVITY

S. A. HESSEIN

Chemistry Department, Faculty of Science (Girl's), Al-Azhar University, Cairo, Egypt

Abstract

Treatment of 1-[6-hydroxy-4-methoxybenzofuran-5-yl]ethanone **(1)** with cinnamaldehyde gave 1-[6-hydroxy-4-methoxybenzofuran-5-yl]-5-phenylpenta-2,4-diene-1-one **(2)** which reacted with formaline and 4-chloroniline to give benzofuran derivative **(3)** according to Mannich reaction. Interaction of **2** with 20% of sulphuric acid, malononitrile, ethylcyano acetate, phenyl hydrazine and guanidine hydrochloride afforded the corresponding furo[3,2-g]chromon-5-one **(4),** pyridine, pyrazole and pyrimidine derivatives **(5-8)**. Also, compound **8** reacted with phosphorus-oxychloride in dimethyl formamide and p-flurobenzylidenemalononitrile to give formyl and pyrimidopyrimidene derivatives (**10, 12**).

Introduction

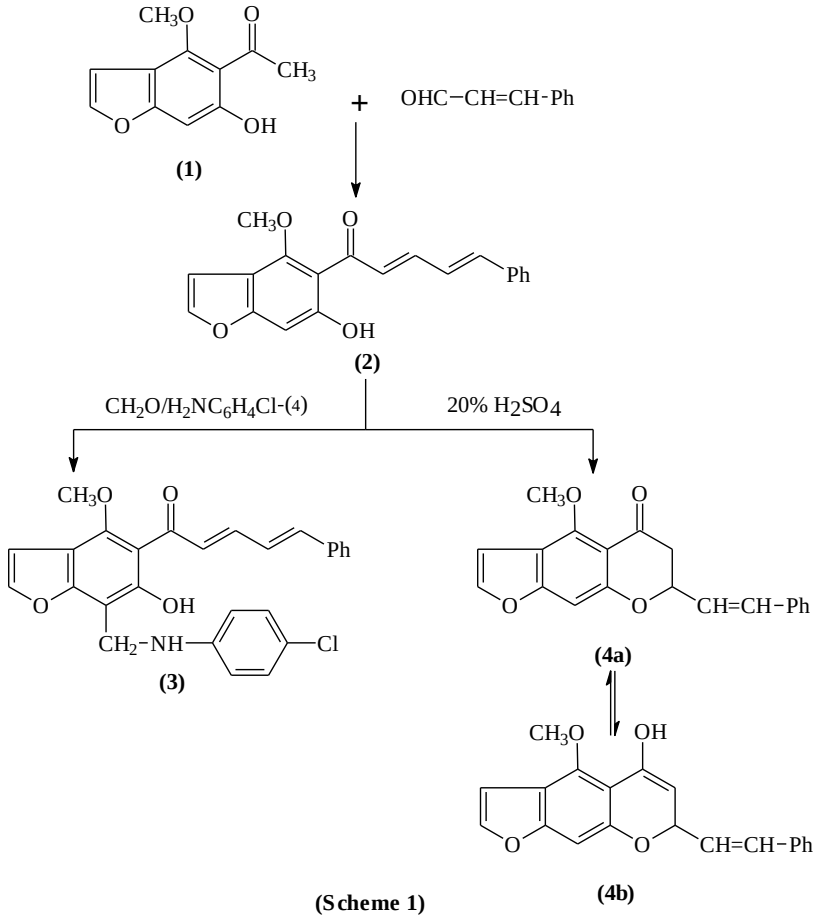
It is well known that benzofuran derivatives show marked biological activity[1-6]. Also, derivatives of pyridine, pyrimidine and pyrazol show a varity of pharmacological effects[7,8]. Thus, the aim of the present work is synthesis pyridine, pyrimidine and pyrazole containing benzofuranyl moiety to investigate their potential activity.

Result and discussion

Reaction of 1-[6-hydroxy-4-methoxybenzofuran-5-yl]ethanone **(1)** with cinnamaldehyde led to form 1-[6-hydroxy-4-methoxybenzofuran-5-yl]-5-phenylpenta-2,4-diene-1-one **(2)** Scheme (1). Compound **2** was established by correct analytical and spectral data. The mass spectrum afforded a molecular ion peak at m/z 320 [M^+, 50%] with a base peak at 190 and the following observed peaks at 277 (20.2%), 230 (16.3%), 164 (38.04%), 148 (20.6%) and 117 (16.3%) which compatible with molecular formula $C_{20}H_{16}O_4$ Chart (1).

According to Mannich reaction **2** was reacted with 4-chloroaniline and formaline to yield Mannich base **(3)** Scheme (1). The mass spectrum of **3** exhibited a molecular ion peak M^+ at m/z 459 (2.8%), corresponding to molecular formula $C_{27}H_{22}NO_4Cl$ and this was in agreement with previous work[9-12].

When hydroxychalcone **2** was refluxed with 20% sulphuric acid, cyclization occurred to form furo[3,2-g]chromon-5-one **(4a-4b)** or the possible isomers Scheme (1). The IR spectrum of compound **4** revealed the presence of carbonyl group of γ-pyrone at 1620 cm^{-1}, and this analogy with previous work[5,13].

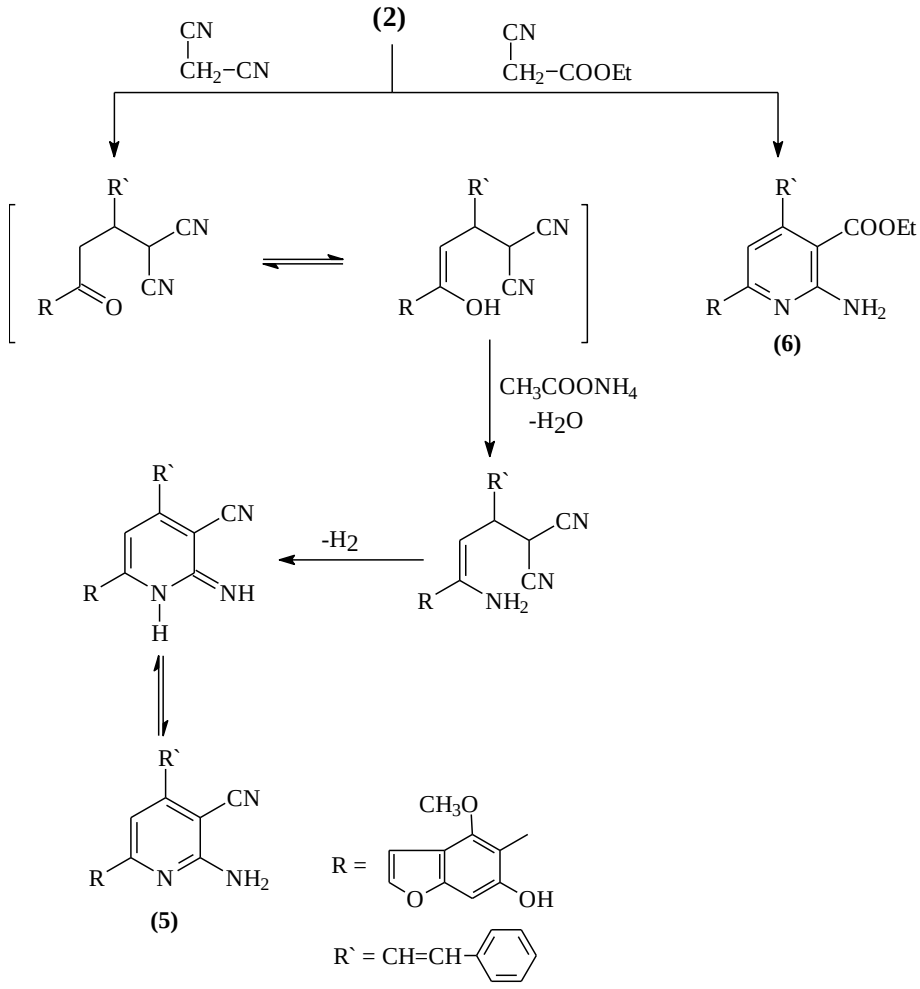


(Scheme 1)

Treatment of **2** with malononitrile led to the formation of pyridin-3-carbonitrile or the possible isomer **(5a-5b)**. The reaction can proceeded via chalcone **(2)** which reacted instantaneously with malononitrile through Michael reaction, then cyclization occurred via elimination of molecule of water and dehydrogenation Scheme (2). The assigned structure was in agreement with analytical and spectral data where IR spectrum exhibited bands at 2194 (CN), 3049, 3190 (NH_2) and 3340 (OH) groups. While ^{1}H-NMR of **5** (DMSO) showed signals at δ 4.00-4.19 (m, 5H,

OCH_3 + NH_2), 6.7 (, 1H, H-3 furan moiety), 6.72-7.82 (m, 10H, 1H, H-5 pyridine + Ar-H + 2H, olefinic + H-2 furan moiety) and at 11.98 (, 1H, OH, exchangeable with D_2O).

Similarly **2** reacted with ethylcyanoacetate to produce pyridin-3-ethyl carboxylate **(6)** Scheme (2). IR spectrum afforded bands at 1743 (C=O), 3028 & 3236 (NH_2) and at 3286 (OH) groups and this was analogy with previous work[14].



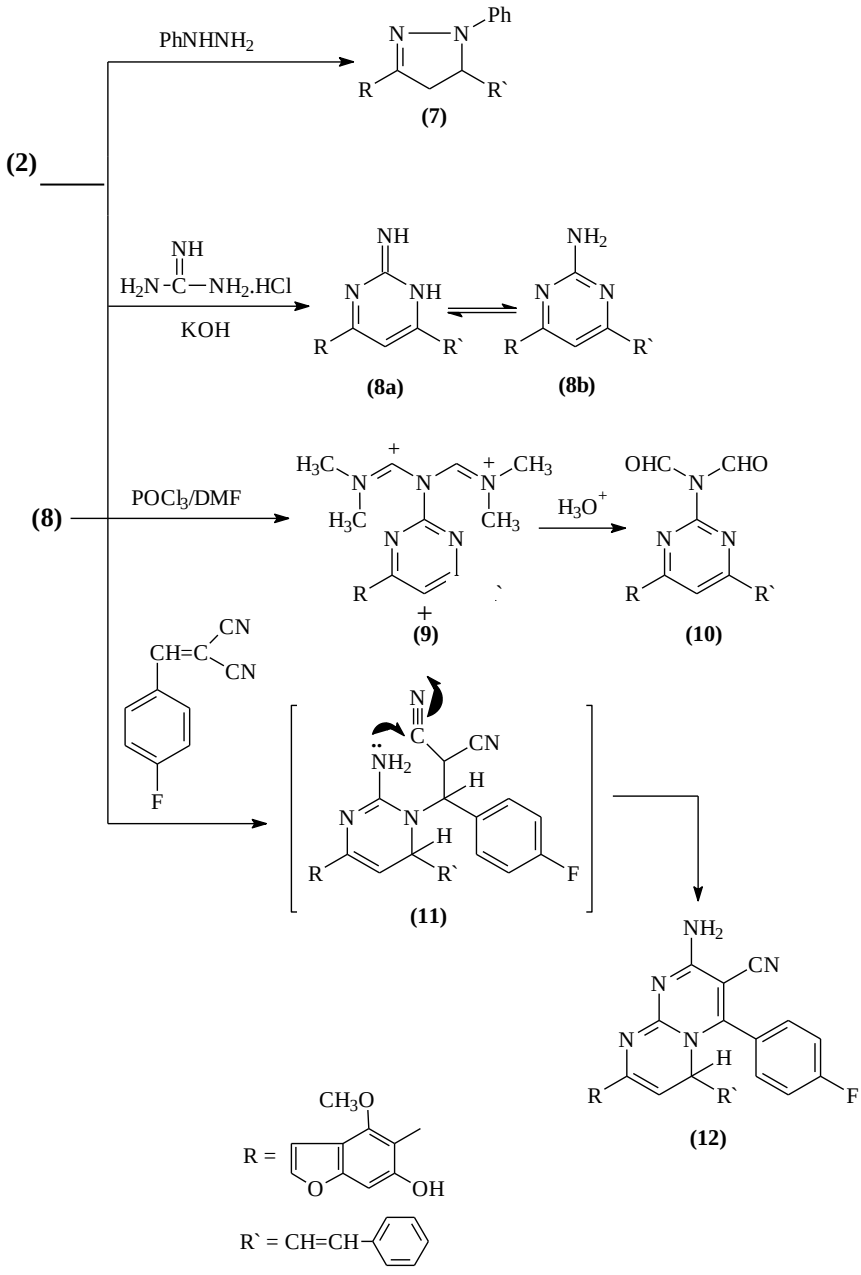
(Scheme 2)

Compound **2** was reacted with phenylhydrazine to form pyrazole derivative (**7**) scheme (**3**). Structure **7** was established by correct analytical and spectral data where IR showed disappearance of carbonyl group found in the parent compound and revealed bands at 1601, 3313 for (C=N) and (OH) groups, respectively.

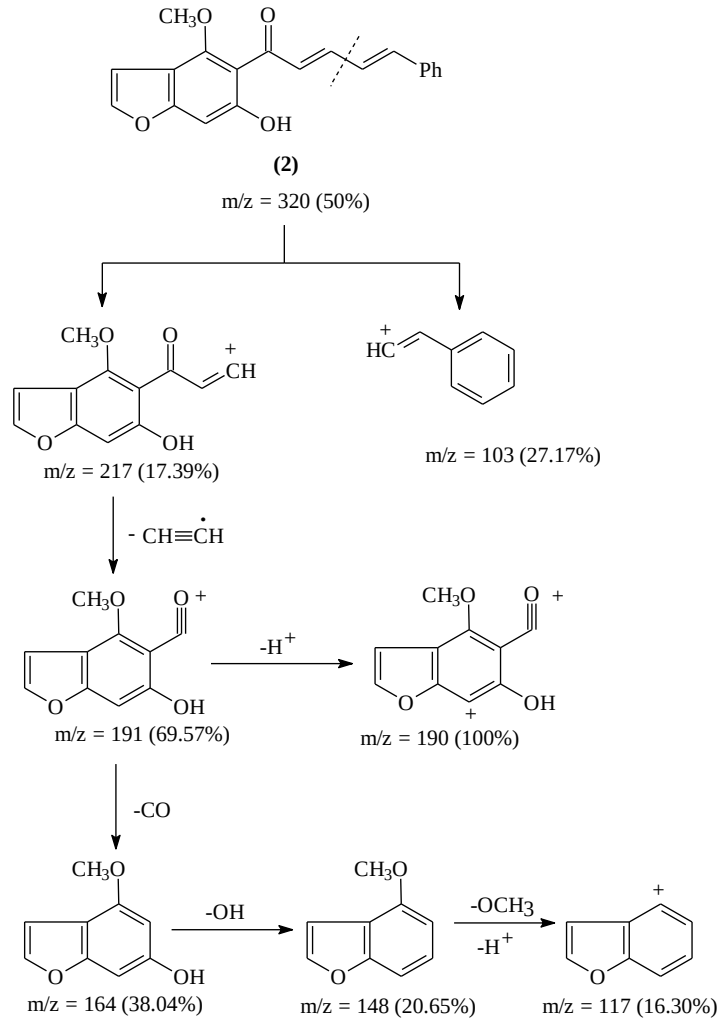
Furthermore, the reaction of **2** towards binucleophilic reagent was investigated. Thus, interaction of **2** with guanidine hydrochloride in the presence of potassium hydroxide resulted pyrimidine derivative or its possible isomer (**8a-8b**) Scheme (3). The reaction was proceeding via Michael addition followed intramolecular cyclization followed by water elimination. IR spectrum of **8** showed the disappearance of carbonyl group which found in the parent compound and showed bands at 3124 & 3164 for NH_2 and 3413 for OH groups.

In addition, treatment of **8** with phosphorusoxychloride in dimethylformamide, the formyl derivative (**10**) was obtained via vilsmeier reaction, Scheme (**3**). The proposed structure 10 was based on elemental analysis and IR spectrum which revealed the lack of NH function group and the presence of C-H aldehyde at 2866 & 2927 and OH group at 3327. The mass spectrum exhibited a molecular ion peak at m/z 415 which corresponding to the molecular formula $C_{23}H_{17}N_3O_5$.

Further, compound **8** reacted with p-flurobenzylidene malononitrile in the presence of catalytic amount of piperidine to afford pyrimido-pyrimidine derivative (**12**), via Michael adduct (**11**) followed by intramolecular cyclization , Scheme (**3**). The structure of compound **12** was esablished by elemental analysis and IR spectrum showed the absorption bands at 2190 cm^{-1} (C≡N), 3124 & 3192 (NH_2) and at 3397 (OH) groups.


PhNHNH2
(7)
(2)
NH
H2N-C-NH2.HCl
KOH
(8a)
(8b)
(8)
POCl3/DMF
H3O+
(9)
(10)
CH=C(CN)CN
F
(11)
(12)
CH3O
R =
OH
R` = CH=CH-

(Scheme 3)



(Chart 1)

Antimicrobial activity of some new benzofuran derivatives:-

The standardized disc-agar diffusion method (Bauer-Kirby 1966)[15] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphlococcus aureus* (ATCC 25923) and *Streptococcus pyogenes* (ATCC 19615) as Gram positive bacteria, *Pseudomonas fluorescens* (S 97) and *Pseudomonas phaseolicola* (GSPB 2828) as Gram- negative bacteria and the fungi *Fusarium oxysporum* and *Aspergillus fumigatus.*

The broad spectrum antibiotic chloramphencol was used as standard antibacterial reference and cyclohexamide was used as standard antifungal reference.

The tested compounds were dissolved in dimethyl formamide [(DMF) which have no inhibition activity] to get concentrations of 2 mg/ ml and 1 mg/ ml. The test was contain infusion of 200 g potatoes, 6g dextrose agar.

Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 μl) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface.

After incubation for 36 h at 27°C in the case of bacteria and for 48 h at 24°C in the case of fungi inhibition of the organisms which evidenced by clear zone surround each disk was measured and used to calculate mean of inhibition zones, (Table 2).

The antimicrobial investigation revealed that the compound (**2**) showed slight activity against gram positive, gram negative bacteria and fungi, compound (**4**) showed slight activity against gram negative bacteria, compound (**5**) was completely in active against bacteria strain but high activity against fungi. Compound (**7**) afforded slight activity against gram positive and gram negative bacteria and completely in active against fungi.

In addition compound (**8**) showed intermediate activity against gram negative bacteria and slight activity against fungi, while compound **10** showed high activity against gram positive and gram negative bacteria. This may be due to the presence of pyrimidine moiety.

Experimental

All melting points were uncorrected. The IR spectra were recorded on pye unicam sp 11100 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or in DMSO on a varian 90, 200 MHz, spectrometer. Mass spectra were preformed by a shimadzu Gc-MS-QP 100 Ex (shimadzu, Japan). Elemental analysis were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University.

1-[6-hydroxy-4-methoxy benzofuran-5-yl]-5-phenylpenta-2,4-dien-1-one (2)

To a solution of **1** (3.2 gm, 0.01 mol) and cinamaldehyde (0.01 mol) in ethanol (30 ml) was added 10% alcoholic sodium hydroxide (5 ml) and the reaction mixture

was stirred at room temperature for 30 mint. The reaction mixture was acidified with hydrochloric acid and the resulting solid was washed with water and crystallized from ethanol to give **2** (Table 1).

1-[7-(4-chlorophenyl)aminomethyl-6-hydroxy-4-methoxybenzo-furan-5 yl]phenylpenta-2,4-dien-1-one (3)

To a solution of compound **2** (3.2 gm, 0.01 mol) in ethanol (30 ml), 4-chloroaniline (1.3 gm, 0.01 mole) and CH_2O 40% formaldehyde (0.015 mol) were added with stirring for 30 min. and cooling between 0-5°c. The reaction mixture was left for one hour, the solid so formed was collected and crystallized from acetone to form **3**, Table (1). MS. 459 (M^+, 2%) with a base peak at 89 and the following observed peaks at 416 (1.21%), 369 (1.9%), 311 (65.6%), 239 (4%), 177 (12.1%) and 133 67.9%).

6,7-dihydro-4-methoxy-7-styrylfuro[3,2-g]chromon-5-one (4)

A solution of **2** (3.2 gm, 0.01 mol) in ethanol (20 ml) and concentrated sulfuric acid (2 ml) was refluxed for about 4 hrs. Evaporate the solvent and the resulting solid was crystallized from n-hexane to give **4** which gave no colour reaction with ferric chloride solution. ^{1}H NMR (DMSO) δ 3.96 ppm (1s, 3H, OCH_3), 6.69-8.007 (m, 10H, Ar-H + 2=CH + H-2 chromon + H-3 furan) (J = 2.02 Hz), δ 9.06 (d, 1H-2 furan) (J = 2.10 Hz), δ 9.73 (s, 1H, H-3 Chromon) and δ 10.10 (s, 1H, OH) (keto enol form).

2-Amino-6-[6-hydroxy-4-methoxybenzofuran-5-yl]-4-styrylpyridin-3-carbonitrile (5)

A mixture of compound **2** (3.2 gm, 0.01 mol) malononitrile (0.66 gm, 0.01mol) and ammonium acetate (0.77 gm, 0.02 mol) was fused at 100°C for 1 hour, then allowed to cool and poured into ethanol. The solid product was collected and crystallized from ethanol to give **5** (Table 1).

Ethyl 2-Amino-6-[6-hydroxy-4-methoxybenzofuran-5-yl]-4-styryl-pyridin-3-carboxylate (6)

A mixture of compound **2** (3.2 gm, 0.01 mol) ethylcyano acetate (0.01 mol) and a few drops of ammonium acetate in ethanol (30 ml) was refluxed for 3 hours, then allowed to cool. The solid product was collected and crystallized from n-hexane to give **6** Table (1).

5-(4,5-dihydro-1-phenyl-5-styryl-1H-pyrazol-3-yl)-4-methoxybenzo-furan-6-ol (7)

A solution of **2** (3.2 gm, 0.01 mol) and phenyl hydrazine (0.01 mole) in ethanol (30 ml) was refluxed for 4 hours. The solid so obtained was crystallized from ethanol to give **7** Table (1). ^{1}H NMR ($CDCl_3$): δ 2.43 (d, 2H, pyrazol moiety), δ 4.24 (1s, 3H, OCH_3), 6.79-7.47 (m, 16H, Ar-H + 2 = CH + CH of pyrazol + H-3, H-2 furan) and δ 10.92 (br, 1H, OH).

5-(2-amino-4-styrylpyrimidin-4-yl)-4-methoxybenzofuran-6-ol (8)

A mixture of **2** (3.2 gm, 0.01 mol) guanidine hydrochloride (0.59 gm, 0.01 mol) and potassium hydroxide (0.5 gm) in ethanol (50 ml) was refluxed 4 hours, then allowed to cool. The solid product was collected and crystallized from ethanol to produce **8** (Table 1).

N-formyl-N-[4-(6-hydroxy-4-methoxybenzofuran-5-yl)-6-styryl-pyrimidin-2-yl]formamide (10)

To a solution of **8** (3.59 gm, 0.01 mol) in 30 ml of dry N,N-di-methylformamide, phosphorus oxychloride (0.02 mol) was added under stirring for about 30 min. in an ice bath then the solution was poured into 200 ml H_2O. The solid product obtained was collected and recrystallized from ethanol to give **10** (Table 1). MS (10) 415 (M^+, 3.4%) with a base peak at 283, and the following observed peaks at 345 (8.1%) 327 (3.07%), 309 (45.9%), 269 (2.84%) 141 (6.12%) and 133 (54.8%).

2-amino-4-(4-flurophenyl)-8-[6-hydroxy-4-methoxybenzofuran-5-yl]-6-styryl 6H-pyrimido[1,2-a]pyrimidin-3-carbonitrile (12)

A mixture of **8** (3.2 gm, 0.01mole), p-flurobenzylidene malo-nonitrile (1.72 gm, 0.01 mole) and piperidine (0.5 ml) in ethanol (30 ml) was refluxed for 3 hours, then allowed to cool. The solid product was collected and crystallized from ethanol to give **12**, Table (1). Ms (12) showed a molecular ion M^+ at m/e fragment 442 [M^+-89 (ph-C≡), 57%), with a base peak at 109 and the following peaks at 313 (19%), 269 (41.3%), 230 (19%), 190 (23%) and 90 (38.1%).

Table (1): Characteristics data for the prepared compounds

Comp. No	M.P. [°C]	Yield %	Mol. formula (M. wt)	Elemental analysis Calcd./found		
				C	H	N
2	100-2	87	$C_{20}H_{16}O_4$ (320.344)	74.98 74.99	5.03 5.04	
3	318-20	97	$C_{27}H_{22}ClNO_4$ (459.929)	70.51 70.52	4.82 4.83	3.04 3.05
4	90-92	62	$C_{20}H_{16}O_4$ (320.344)	74.98 74.97	5.03 5.02	
5	98-100	82	$C_{23}H_{17}N_3O_3$ (383.407)	72.05 72.11	4.46 4.51	10.95 11.10
6	82-4	46	$C_{25}H_{22}N_2O_5$ (430.46)	69.75 69.76	5.15 5.16	6.50 6.51
7	73-5	77	$C_{26}H_{22}N_2O_3$ (410.473)	76.07 76.08	5.40 5.42	6.82 6.84
8	100-101	75	$C_{21}H_{17}N_3O_3$ (359.385)	70.18 70.15	4.76 4.78	11.69 11.67
10	148-50	93	$C_{23}H_{17}N_3O_5$ (415.405)	66.50 66.52	4.12 4.13	10.11 10.12
12	114-116	80	$C_{31}H_{22}FN_5O_3$ (531.547)	70.04 70.05	4.17 4.21	13.17 13.18

Table (2): Antimicrobial activity of some new benzofuran derivatives.

Organism	Mean* of zone diameter, nearest whole mm.											
	Gram-positive bacteria				Gram-negative bacteria				Fungi**			
	Staphylococcus aureus (ATCC 25923)		*Streptococcus Pyogenes* (ATCC 19615)		*Pseudomonas phaseolicola* (GSPB 2828)		*Pseudomonas fluorescens* (S 97)		*Fusarium oxysporum*		*Aspergillus fumigatus*	
Consent	1	2	1	2	1	2	1	2	1	2	1	2
Sample	2 mg/ml	1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml	1 mg/ml
2	14, L	9, L	17, I	10, I	6, L	4, L	-	-	5, L	3, L	-	-
4	-	-	-	-	7, L	4, L	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	34, H	23, H	29, H	17, H
7	15, L	9, L	16, I	9, L	9, L	5, L	-	-	-	-	-	-
8	-	-	-	-	18, I	10, I	16, I	7, L	6, L	3, L	-	-
10	32, H	21, H	20, I	12, I	23, H	19, H	27, H	24, H	-	-	-	-
Control	42	28	38	30	36	25	38	30	40	28	40	31

* = Calculate from 3 values ** = Identified depending on morphological and microscopical characters
- = No effect
L = Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of control
I = Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of control
H = High activity = Mean of zone diameter > 2/3 of mean zone diameter of control
# = Chloramphencol in the case of bacteria and cicloheximide in the case of fungi

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الملخص العربى

تشييد بعض مشتقات البنزوفيوران الجديدة المتوقع لها نشاط بيولوجى

سعدية على حسين

كلية العلوم (بنات)-جامعة الأزهر – مدينة نصر – القاهرة – مصر

بمعالجة 1-[6-هيدروكسى-4-ميثوكسى بنزوفيوران-5-يل]ايثانون مع السنامالدهيد نتج 1-[6-هيدروكسى-4-ميثوكسى بنزوفيوران-5-يل]-5-فينيل بنتا-2،4-دايين-1-اون الذى يتفاعل مع 4-كلوروانيلين والفورمالين ليعطى مشتقا من قواعد مانش بينما بتفاعله مع 20% من حمض الكبريتيك المركز والمالونونيتريل والايثيل سيانواسيتات والفينيل هيدرازين والجواندين هيدروكلوريد نتج فيورو[3,2-g]كرومون-5-اون ، البيريدين، البيرازول والبيريميدين المقابل. وعند تفاعل البيريميدين مع ثالث اوكسى كلوريد الفوسفور وبارا فلورو بنزيليدين مالونونيتريل امكن الحصول على مشتقات الفورميل وبيريميدوبيريميدين.

وقد تم اثبات التركيب البنائى للمركبات الجديدة بواسطة طيف الاشعة الحمراء و الرنيين النووى المغناطيسى وطيف الكتلة.

كما تم اختبار النشاط البيولوجى لبعض المركبات المحضرة حديثا ووجد ان لبعضها نشاطا ملحوظا.