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SYNTHESIS OF SOME NOVEL PYRIDINE, THIOPHENE, THIENOPYRIMIDINE AND THIENOPYRIDINE DERIVATIVES CONTAINING BENZOFURANYL MOIETY

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Abstract

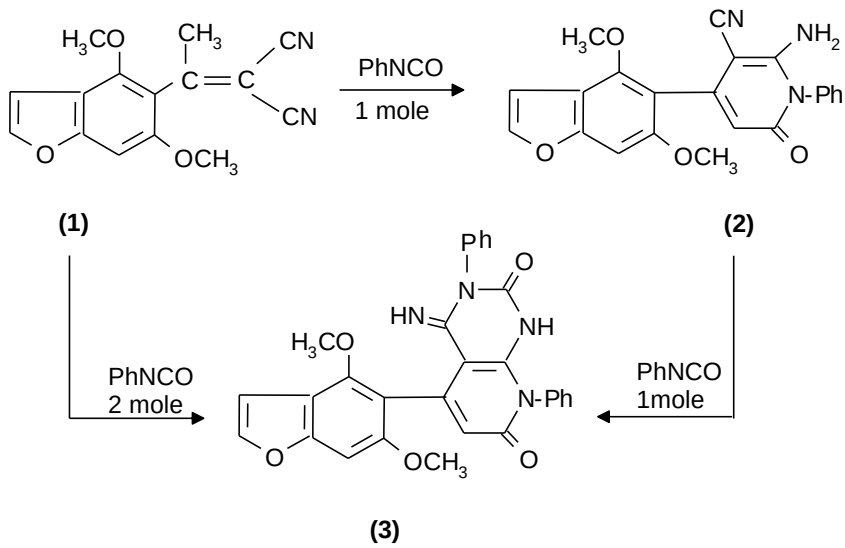
Interaction of 2-[1-(4,6-dimethoxybenzofuran-5-yl)ethylidine]malononitrile **(1)** with phenylisocyanate, phenylhydrazine, carbon disulphide and arylidenemalono-nitrile afforded the corresponding pyridine **2**, pyrido[2,3-d] pyrimidine **3**, phenylhydrazone **4**, pyridine 2,6-dithione **8** and benzene dicarbonitrile **9** derivatives . Treatment of **1** with elemental sulfur under Gewald reaction conditions furnished 2-amino-4-(4,6-dimethoxybenzofuran-5-yl)thiophen-3-carbonitrile **11** which used as starting material in the synthesis of thienopyrimidine **14** and thienopyridine **15** derivatives.

Introduction

Activated nitriles have attracted considerable interest as potential building blocks for many nitrogen containing heterocyclic system[1-3]. Also it is well known that benzofuran derivatives show marked biological activity[4-11]. Thus, the aim of the present work is to synthesis pyridine, thienopyridine, thiophene, pyrrolopyrazole and thienopyrimidine derivatives containing benzofuranyl moiety to investigate their pharma-cological activity.

Results and Discussion

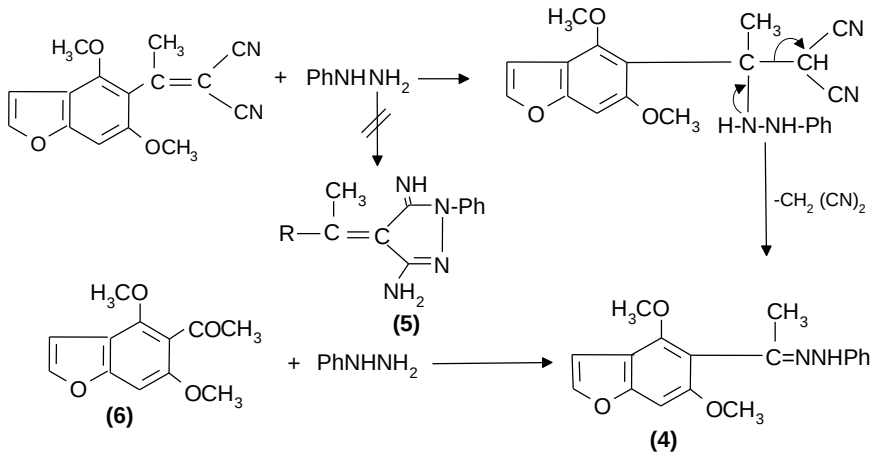
Treatment of 2-[1-(4,6-dimethoxybenzofuran-5-yl)ethylidene]malon-oitrile **(1)**[12,13] with phenylisocyanate provided N-phenyl pyridone derivative **(2)** which reacted with an additional mole of phenylisocyanate to afford pyrido[2,3-d]pyrimidine derivative**(3)**. Compound **3** can be also obtained by reaction of **1** with two moles of phenylisocyanate (Scheme 1).



Scheme (1)

Structure **2** was established by correct analytical and spectral data where IR showed the appearance of amino group at 3327 & 3128 cm^{-1} and carbonyl group at 1700, ^{1}H-NMR revealed the disappearance of methyl group found in parent compound and appeared the signals of phenyl group at δ 6.94-7.26 ppm and mass spectrum exhibited a molecular ion at m/z 387 (M^{+}, 1.42%). While IR spectrum of **3** showed the disappearance of C≡N group and its mass spectrum afforded a molecular ion peak at m/z 506 [M^{+}, 37%] which was compatible with molecular formula $C_{29}H_{22}N_4O_5$ and this was analogy with previous work[14].

On the other hand, when **1** was allowed to react with phenyl hydrazine two products **4** and **5** can be formulated. On the basis of elemental analysis and spectral data structure **5** was readily eliminated. The formation of hydrazone derivative **(4)** was assumed to proceed via nucleophilic addition and subsequent malononitrile eliminated. The proposed structure 4 was supported by independent synthesis from 5-acetyl-(4,6-dimethoxybenzofuran **(6)**[15,16] with phenylhydrazine (m.p. and mixed m.p.) (Scheme 2).



(Scheme 2)

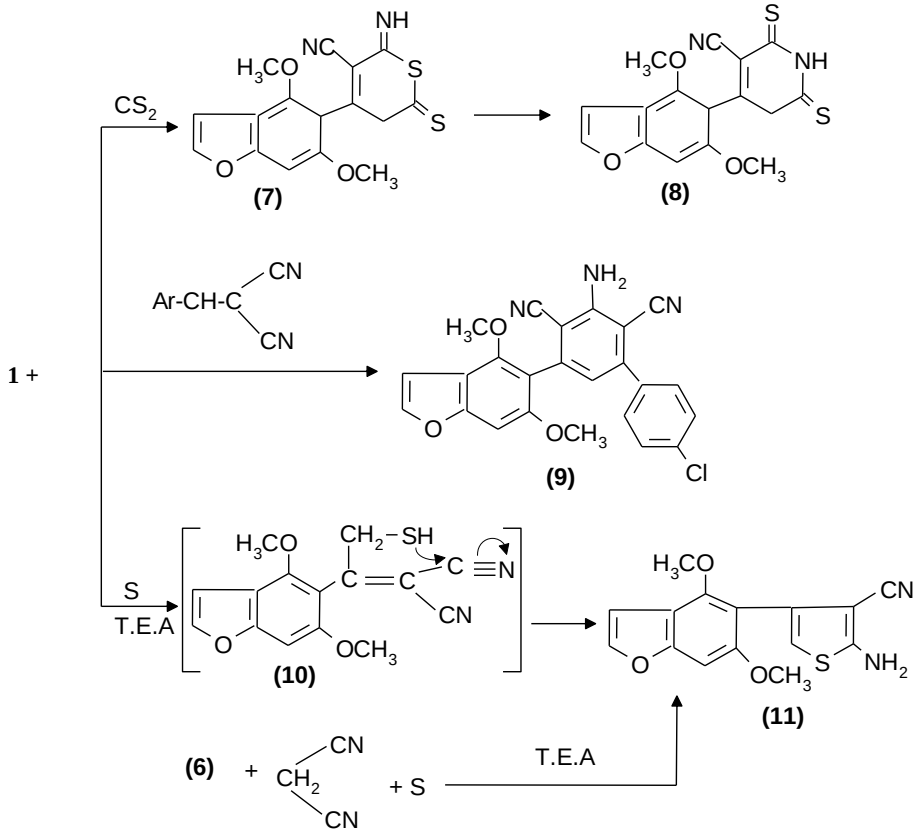
The reactivity of methyl function in compound **1** towards carbon disulphide, arylidene malonitrile and sulfur were investigated. Thus, interaction of **1** with carbon disulphide yielded thiazine derivative **(7)** which rearranged into pyridine-2,6-dithione derivative **(8)**. The assigned structure was in agreement with analytical and spectral data where ^{1}H-NMR showed the disappearance of methyl group found in the parent compound and its mass spectrum exhibited a molecular ion peak m/z 344 which was corresponding to the molecular formula $C_{16}H_{12}N_2O_3S_2$ and this was analogy with previous work[17].

Treatment of **1** with 4-chlorobenzylidenemalononitrile furnished 1-amino-5-(4-chlorophenyl)-3-(4,6-dimethoxybenzofuran-5-yl)benzene-2,6-dicarbonitrile **(9)**. Structure **9** was inferred from its elemental analysis and spectral data. The IR spectrum revealed characteristic bands for NH_2 and C ≡ N groups. ^{1}HNMR spectrum in $CDCl_3$ showed the presence of a singlet of H-4 of benzene dicarbonitrile at δ 5.29 ppm multiplet of Ar-H at 7.24–7.56 and revealed the absence of methyl group found in the parent compound. The formation of **9** was assumed to proceed via addition of methyl function of **1** to the activated double bond in 4-chlorobenzylidenemalononitrile to form Micheal adduct which cyclized through HCN elimination (Scheme 3).

Treatment of 1 with elemental sulfur under Gewald reaction conditions[18] furnished 2-amino-5-(4,6-dimethoxybenzofuran-5-yl)thio-phene-3-carbonitrile **(11)**. The formation of compound **(11)** occurred via thiation of methyl group in

compounds **1** to afford **10** as an intermediate followed by interamolecular cyclization (Scheme 3). The structure **11** was proved by the presence of a signal at δ 6.7 ppm characteristic for thiophene proton in ^{1}H-NMR.

Compound **(11)** was also obtained directly by interaction of ketone **6** with a mixture malononitrile and elemental sulfur in presence of few drops of triethylamine (m.p & m. m. p).

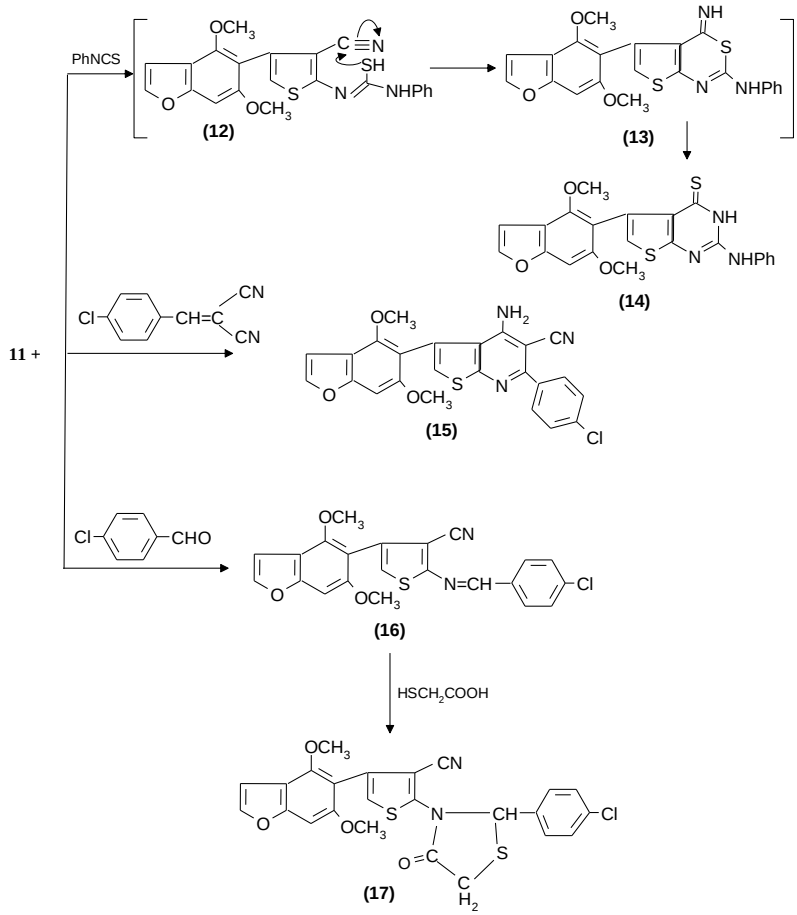


(Scheme 3)

The starting material **11** was proved to be a versatile starting material for the synthesis of some novel theinopyrmidine, and thienopyridine derivatives. Thus, interaction of **11** with phenyliso-thiocyanate in pyridine led to the formation of thiourea intermediate derivative **(12)** which could be cyclized into a product that may be formulated as **13** which rearranged into the most stable isomeric derivatives **(14)**. The mass spectrum of **14** exhibited a molecular ion peak at m/z 435 (M^+, 0.77%) which was compatible to molecular formula $C_{22}H_{17}N_3O_3S_2$ of structure **(14)**.

Further more thienopyridine derivative **(15)** formed when **11** was allowed to react with 4-chlorobenzylidene malononitrile (Scheme 4).

On the other hand; Schiff's base **(16)** was obtained from the reaction of **11** with 4-chlorobenzaldehyde in ethanolic piperidine. IR spectrum showed the disappearance of NH_2 group and presence of (C ≡ N) group at 2206 cm^{-1}. ^{1}H-NMR afforded signals at δ 6.47 ppm (s, 1H, thiophene, and δ 8.71 (s, 1H, N=CH). Treatment of **16** with mercapto-acetic acid yielded the corresponding 2-(2-[4-chlorphenyl]-4-oxo thiazolidin-3-yl)-5-(4,6-dimethoxybenzofuran-5-yl)thiophen-3-amine **(17)**. The assigned structure was in agreement with correct elemental analysis and spectral data where IR spectrum revealed bands at 1701 & 2202 for (C=O) and (C≡N) groups respectively.



(Scheme 4)

Experimental

All melting points were uncorrected. The IR-spectra were recorded on Pye unicam sp/1100 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or in DMSO on a varian 90, 200MHz. Spectrometer. Mass spectra were performed 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. The characteristics data for the prepared compounds were given in Table (1).

2-Amino-1,6-dihydro-4-(4,6-dimethoxyfuran-5-yl)-6-oxo-1-phenylpyridine-3-carbonitrile (2):

A solution of **1** (3.9 g 0.01 mol) and phenyl isocyanate (1.19 gm, 0.01 mol) in pyridine (20 ml) was refluxed for 8h then allowed to cool. The precipitate was filtered off and crystallized from ethanol to give 2 Table (1). IR: 3327, 3128 (NH_2), 2207 (C≡N), 1700 (C=O). ^{1}H-NMR ($CDCl_3$): δ3.82 & 4.06 ppm (2s, 6H, $2OCH_3$), 6.05 (s,1H, H_3 pyridone moiety), 6.77 (s,1H, H-7 benzofuran moiety), 6.87 (d, 1H,H_{-3} furan) (J=2.02 Hz), 6.94 –7.50 (m,7H, Ar-H + NH_2) and 7.59 (d, 1H,H_{-2} furan moiety) (J=2.10Hz). MS: 387 (M^+, 1.42%), 236 (1.2%), 204 (100%), 132 (7.3%), 118 (3.2%), 107 (2.2%) and 67 (4%).

3,4-dihydro-4-imino-5-(4,6-dimethoxybenzofuran-5-yl)-3,8-diphenyl pyrido [2,3-d] pyrimidine 2,7 (1H, 8H) dione (3):

A solution of **(1)** (3.9 gm 0.01 mol) and phenylisocyanate (2.38 gm, 0.02 mol) in pyridine (20 ml) was refluxed for 12h. then allowed to cool. The precipitate was filtered off and crystallized from acetic acid to give 3. Table (1) IR : 3127 & 3118 (NH), a strong band at 1700 (C=O) groups. MS : 506 (M^+, 37%) with a base peak at 72, and the following observed peaks at 328 (35%), 284 (30.2%), 269 (27.9%), 252 (40%), 241 (32.5%), 209 (44%), 181 (32.5%) and 124 (62.7%).

Compound 3 was also obtained by refluxed (2), (3.87 gm, 0.01 mol) with phenylisocyanate (1.19 gm, 0.01 mol) in pyridine (30 ml) for 6h.

2-[4,6-dimehoxybenzofuran-5-yl ethylidene] phenyl hydrazone (4):

A solution of **1**, (3.9gm, 0.01 mol) and phenyl hydrazine (3.08 g, 0.01 mol) in ethanol (50 ml) was refluxed for 2h. The solid obtained was crystallized from n-hexane to give 4. Table (1). IR: 3128 cm^{-1}(NH), 1619 (C=N). ^{1}H-NMR ($CDCl_3$), δ2.51ppm (s,3H,CH_3) , 3.82, 4.06 (2s, 6H, $2OCH_3$), 6.76 (d,1H, H-3 furan moiety)

(J=2.02Hz), 6.86 (s,1H,H–7), 7.01-7.45 (m. 6H,Ar-H + NH) and 7.50(d,1H,H-2) furan moiety) (J= 2.10 Hz).

Compound 4 can be also obtained by refluxed (4.6-dimethoxy-benzofuran-5-yl) methyl ketone (6) 0.66 gm, 0.01 mol) and phenyl hydrazine (1.19 gm, 0.01 mol) in ethanol (40 ml) for 2h.

4-(4,6-dimethoxybenzofuran-5-yl)-3-cyanopyridin-2,6-dithione (8):

To a solution of **(1)** (3.9, 0.01 mol) in pyridine (5 ml), carbon disulphide was added and the solution was heated under refluxed for 8h in water bath. After cooling methanol (30ml) was added and the solid separated was washed with P.E 80-100ºC then crystallized from ethanol to give **8** (Table 1). IR : 3133cm^{-1} (NH), 2231 (C≡N) 1146 (C=S). ^{1}H-NMR ($CDCl_3$) δ 3.82 & 4.06 ppm (2s, 6H, $2OCH_3$), 4.14 (s,2H,CH_2), 6.76 (d, 1H, H-3 furan moiety) (J=2.01Hz), 6.91 (s, 1H,Ar,H), 7.48 (d, 1H,H-2 furan moiety) (J=2.00Hz) and 7.51 (s, 1H, NH-exchangeable with D_2O). MS : 344 (M^+,1.02%) and a base peak at 269.

1-amino-3-(4-chlorophenyl)-5-(4,6-dimethoxy-benzofuran-5-yl) benzene-2,6-dicarbonitrile (9).

A solution of **(1)** (3.9 gm, 0.01 mol) and 4-chlorobenzlidene malononitrile (1.88 g, 0.01 mol) in ethanol (30 ml) in presence of few drops of piperidine was refluxed for 3h. Then the solid obtained filtered then crystallized from P.E. 80-100ºC. to give 9. (Table 1). IR 3355, 3232 cm^{-1} (NH_2), 2215 & 2190 (2C≡N) ^{1}H-NMR ($CDCl_3$). δ 3.80 & 4.0ppm (2,s, 6H, $2OCH_3$), 5.29 (s,1H,H-4 of benzene dicarbonitrile), 6.78 (d,1H,H-3 furan moiety) (J=2.2Hz) 6.87 (s,1H,H-7 benzofuran moiety) and 7.24-7.56 (m, 7H, Ar-H+NH_2 + H-2 furan moiety).

2-amino-5-(4,6-dimethoxybenzofuran-5-yl)thiophen-3-carbonitrile (11):

Method A :

A solution of **(1)** (3.9 g, 0.01 mole) and sulfur powder (0.32 gm 0.01 mole) in ethanol (50 ml) containing drops of piperidine, was refluxed for 3h. the reaction mixture was cooled filtered the resulting solid was crystallized from ethanol.

Method B:

A mixture of **(6)**, (2.34 g, 0.01 mol), malononitrile (0.66 gm, 0.01 mol) and sulfur powder (0.32 g, 0.01 mol) was refluxed in ethanol (50 ml) containing few

drops of triethylamine for 2h. Filtrate the mixture, cool and the resulting solid was recrystalized.

IR (11): 3323 & 3221 cm^{-1} (NH_2), 2206 (C≡N). ^{1}H-NMR ($CDCl_3$) : δ 3.75 & 3.95 ppm (2s, 6H, $2OCH_3$) 4.83 (br, 2H, NH_2), 6.29 (s,1H, thiophene moiety) 6.76 (d,1H, H-3 furan moiety) (J= 2.01Hz), 6.84 (s, 1H, Ar-H) and 7.49 (d,1H, H-2 furan moiety) (J=2.22 Hz).

2-Anilino3,4-dihydro-5-(4,6-dimethoxybenzofuran-5-yl)thieno [2,3-d) pyrimidin-4-thione (14):

A solution of **(11)**, (3g, 0.01 mol) and phenyliosthiocyanate (1.19g 0.01 mol) in dioxane (20ml) was refluxed for 5h. The solvent was distilled off and the solid product which formed on cooling was isolated by filteration and identified as **14**. (Table 1) IR 3214 & 3117 cm^{-1} (NH), 1596 (C=N), 1199 (C=S): MS: 435 (0.77%) with a base peak at 181 and significant peaks at 154 (3.4%), 137 (2%), 108 (1.1%) and 94 (5%).

4-Amino–3-cyano-2-(4-chlorphenyl)-5-(4,6-dimethoxybenzofuran-5-yl)-thieno [2,3-b] pyridine (15):

Equimolar amounts of **(11)** (0.3 g, 0.01 mol) and 4-chloro-benzylidenemalonitrile (1.89 g, 0.01 mol) was refluxed in dioxane (30ml) in presence of few drops of piperidine for 3h. Then the solvent was concentrated, the solid obtained was crystallized from P.E-60-80ºC to give 15 (Table 1). IR 3420 & 3327 cm^{-1} (NH_2), 2204 (C≡N). ^{1}H-NMR ($CDCl_3$). δ 3.83 & 4.06 ppm (2s, 6H, $2OCH_3$), 5.96 (s,1H,thiophene moiety), 6.76 (d,1H,H-3 furan moiety) (J=2.202Hz), 6.86 (s,1H, H-7 benzofuran moiety) and 7.24-7.50 (m, 7H, Ar-H+NH_2 + H-2 furan moiety).

2-(4-chlorobenzylidene amin)-4-(4,6-dimethoxy-benzofuran-5-yl)

thiophen –3-crabonitrile (16):

A solution of **(11)** (3.0 g 0.01 mol) and 4-chlorobenzoldehyde (1.45 g, 0.01 mol) in ethanol (20 ml) containing few drops of piperidine was refluxed for 4h. The solvent was removed and the solid obtained was crystallized from n hexane (Table 1). I.R. 2190 (C≡N), 1609 (C=N). ^{1}H-NMR ($CDCl_3$) δ 3.99 & 4.18 ppm (2 s, 6H, $2OCH_3$), 6.47 (s,1H, thiophene moiety), 6. 95-8.11 (m, 7H,Ar-H+ furan protons) and 8.71(s,1H,N=CH).

2-(2-[4-chlorphenyl] 4-oxo-thiozolidin-3yl)-5- (4,6-dimethoxybenzo-furan-5-yl) thiophen-3-amine (17):

A solution of **(16)** (4.22, 0.01 mol) and mercaptoacetic acid (0.92 g, 0.01 mol) in dry benzene (50 ml) was refluxed for 6h. The resulting solid washed with petroleum ether and crystallized from ethanol to give **17** (Table 1). IR 2202 (C≡N), 1701 (C=O). ^{1}H-NMR (DMSO) δ3.92 & 4.06 ppm (2s,6H, 2OCH_3, 4.91-4.95 (s, 3H, thiazolidine moiety), 6.35 (s,1H, thiophene) and 6.75-7.60 (m, 7H, Ar-H + furan protons).

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	104-5	40	$C_{22}H_{17}N_3O_4$ (387)	68.21 68.16	4.42 4.40	10.84 10.79
3	130-2	67	$C_{29}H_{22}N_4O_5$ (506)	68.76 68.75	4.37 4.36	11.06 11.10
4	60-1	70	$C_{17}H_{18}N_2O_3$ (298)	68.44 68.42	6.08 6.10	9.38 9.35
8	105-6	68	$C_{16}H_{12}N_2O_3S_2$ (344)	55.79 55.80	3.51 3.50	8.13 8.11
9	100-2	80	$C_{24}H_{16}N_3O_3Cl$ (429)	67.05 67.10	3.75 3.80	9.77 9.75
11	150-1	57	$C15H_{12}N_2O_3S$ (300)	59.98 59.97	4.02 4.04	9.32 9.34
14	94-5	60	$C_{21}H_{17}N_3O_3S_2$ (435)	57.92 58.00	3.68 3.86	9.63 9.54
15	57-8	87	$C_{24}H_{16}N_3O_3SCl$ (461)	62.40 62.39	3.49 3.48	9.09 9.10
16	85-6	70	$C_{22}H_{15}N_2O_3SCl$ (422)	62.48 62.50	3.57 3.55	6.62 6.59
17	124-5	67	$C_{24}H_{17}N_2O_4SCl$ (496)	58.00 57.98	3.44 3.41	5.63 5.48

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الملخص العربى

تحضير بعض مشتقات البيريدين والبيرولوييريميدين وثينوبيرميدين وثينوبيريدين التى تحتوى على البنزوفيوران

جيهان على مكى ونادية محمد صالح ونادية محمود شميس وسعدية على حسين
قسم الكيمياء كلية العلوم فرع جامعة الأزهر للبنات جامعة الأزهر القاهرة.

عند معالجة [1- (6,4) داى ميثكوكس- 5 بيزوفيورانيل) اثيليدين] مالوتتريل (1) مع الفينيل ابزوسينات (1مول) أعطى مشتق N – فينيل بيرين (2) بينما عند معالجة (1) مع 2 مول من الفينيل ايزوسينات أعطى مشتق بيريدوبيرميدين (3) الذى أمكن الحصول عليه أيضاً من تفاعل (2) مع مول آخر من الفينيل ايزوسينات

- **وتم تفاعل مركب (1) مع الفينيل الهيدرازين ليعطى الهيدرازون المقابل (4) الذى أمكن الحصول عليه أيضاً تفاعل اسيتل (6,4 – ثنائى داى ميثوكسى بزوفيوران مع الفينيل هيدرازين.**

ويتفاعل (1) مع كربون داى سلفيد أمكن الحصول على (8) ، ويتفاعل (1) مع 4 كلورزبزلدين مالوتيزيل تكون (9) بينما تم الحصول على (11) من تفاعل 1 مع الكبريت.
ومن مركب (11) تم الحصول على 14 ، 15، 16 من التفاعل مع الفينيل ايزوسيانات وكلوروبزلدين، مالونونيتريل 4- كلورو بنزالدهيد وقد تم الحصول على مركب 17 بتفاعل 16 مع حمض مركبتواسيتك.

وقد تم إثبات التركيب النباتى للمركبات الجديدة بواسطة طيف الأشعة تحت الحمراء والرنين النووى المغناطيس وطيف الكتلة.