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SYNTHESIS AND REACTIONS OF SOME FURO-PYRIMIDINE DERIVATIVES WITH EXPECTED BIOLOGICAL ACTIVITY

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ABSTRACT

Some condensed furopyrimidines were prepared from 2-ethoxymethylene amino-4,5-di(2-furyl) furane-carbonitrile, with ammonia, phenyl hydrazine, methyl amine, benzyl amine and sodium hydrosulfide. Also furane enaminonitrile was reacted with some isocyanates, isothiocyanates and aromatic aldehydes to produce the corresponding furopyrimidone, urido-, thiouredo- and the Schiff's bases. The structures of the new compounds were established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The biological activity of the compounds was evaluated.

INTRODUCTION

Many condensed heterocyclic systems especially when linked to a pyrimidine ring, play an important role as biologically active compounds [1,2] and pesticides [3].

The furo[2,3-d]-pyrimidine ring system has gained biological interest [4] due to the formal isoelectronic relation between this ring and purine. So, it was of interest to prepare some of their new derivatives to examine their biological activity.

Thus, 2-Amino-4,5-di(2-furyl)furan-3-carbonitrile **1** was the starting nucleous for synthesis of various new compounds . Reaction of **1** with triethyl orthoformate in refluxing acetic anhydride afforded the corresponding 2-ethoxymethylene derivative **2**, its IR revealed no absorption frequency in the NH region . ^{1}H NMR spectrum showed a triplet at . δ 1.6 and a quartet at δ 4.35 assigned to the CH_3 and CH_2 protons of the ethoxy group and a singlet at δ 8.70 ppm due to the methine proton . Ammonia gas was reacted with compound **2** in cold methanol to produce 4-amino-5,6-di(2-furyl)furo[2,3-d]pyrimidine **3** . The structure of **3** was established on bases of correct elemental analysis and IR . Furthermore, the structure of **3** was confirmed by comparison with an authentic sample, prepared by reaction of **1** with formamide [5] (m.p., mixed m.p and Rf values) .

When compound **2** in ethanol was refluxed with hydrazine hydrate or phenyl hydrazine, 4,5-di(2-furyl)-2-(hydrazinomethylene amino)furan-3-carbonitrile **4** and 5,6-di(2-furyl)-4-imino-3H-3-phenylaminofuro[2,3-d]- pyrimidine **5** were obtained, respectively . The IR spectrum of **4** displayed an absorption bands at 2202 cm^{-1} due to the presence of CN . Compound **5** gave correct values for elemental analysis. The IR spectrum displayed absorption at the NH region (3304 cm^{-1}) and showed no absorption at the C≡N region . Also, the structure of **5** was judged by ^{1}H NMR spectrum (DMSO d $_6$), where a broad bands at δ 6.93 and δ 8.00 ppm were assigned to two NH protons and a singlet at δ 8.35 ppm was assigned the pyrimidine proton.

Heating ethanolic solution of **2** with methylamine or benzylamine led to the formation of 3-methyl-5,6-di-(2-furyl)-3H-furo[2,3-d]-pyrimidine-4-imine **6** and 3-benzyl-5,6-di(2-furyl)-3H-furo[2,3-d]-pyrimidine-4-imine **7**, respectively . The IR spectra of **6** and **7** displayed absorption bands at 3446 and 3380 cm^{-1} (NH) .

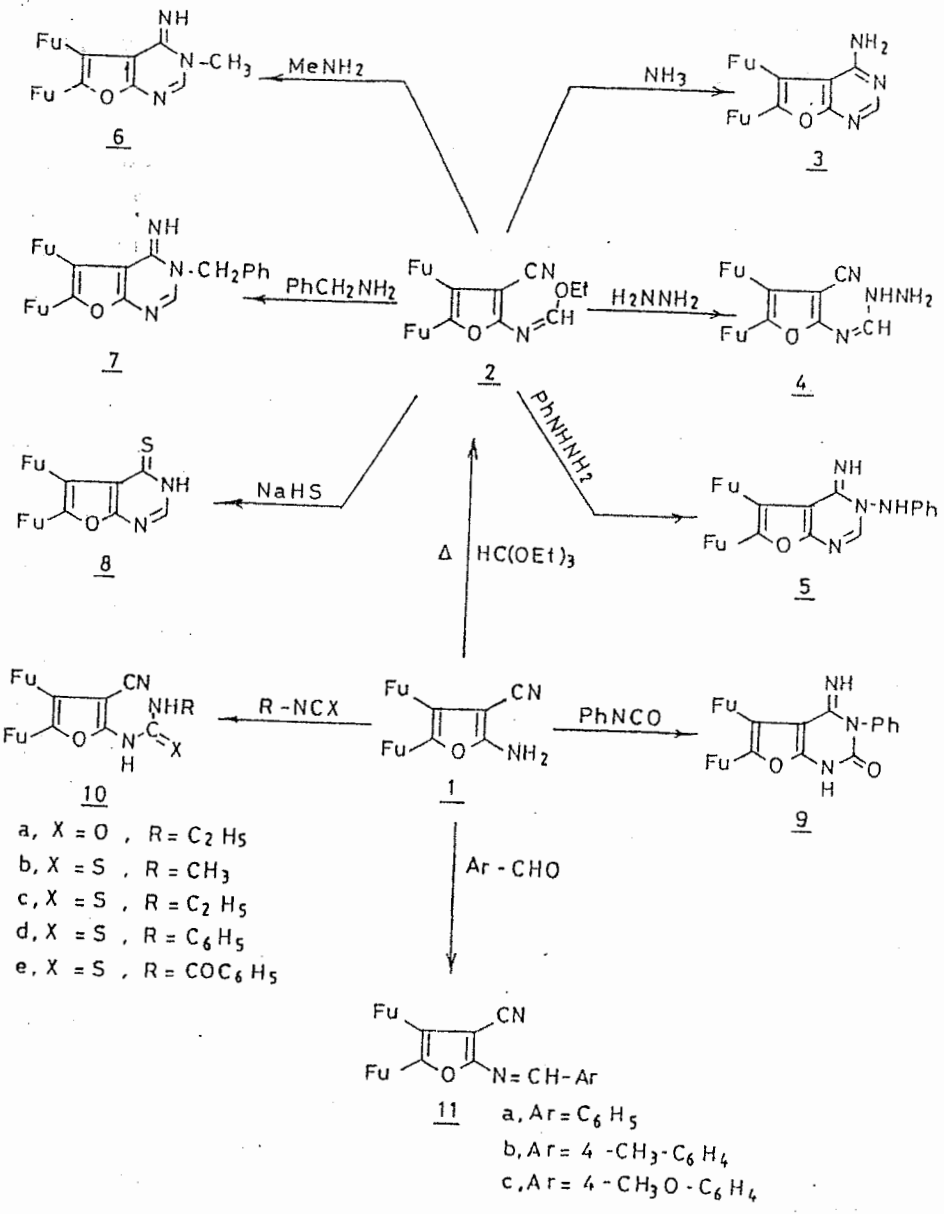
Combination of ^{1}H NMR; ^{13}C NMR[6] for compound 7 (cf. Tables 3&4), mass spectra and correct values for elemental analysis confirmed the cyclized structures **6** and 7 .

Treatment of **2** with sodium hydrosulfide in anhydrous ethanol afforded 5,6-di(2-furyl)-3H-furo[2,3-d]pyrimidine-4-thione **8** . The IR spectrum of **8** displayed absorption bands at 3448 and 1246 cm^{-1} corresponding to the NH and C = S absorption frequencies, respectively . The absorption band of the CN group is absent . The ^{1}H NMR spectrum contained a broad band at δ 7.0 ppm assigned to the NH proton, the mass spectrum was compatible with the given molecular formula $C_{14}H_8N_2O_3S$ (M^+ = m/z 284) .

2-Amino-3-cyano-4,5-di(2-furyl)furan **1** reacted with phenyl-isocyanate in dry toluene, xylene and/or ether under reflux temperature, to give 5,6-di(2-furyl)-1H, 3H-3-phenyl-furo[2,3-d]- pyrimidine-4-imin-2-one **9**.The IR spectrum revealed absorption bands at 3436, 3302 cm^{-1}(NH), 1746 cm^{-1}(C=O) and the absence of the CN band, ^{1}H NMR spectrum showed broad bands at δ 8.65 and δ 7.95 ppm characteristic of two NH protons .

Also, when aminonitrile **1** was reacted with ethyl isocyanate and methyl, ethyl, phenyl, benzoylisothiocyanate it gave the corresponding urido and thiouredo derivatives **10a-e**, respectively . Attempt to obtain cyclized products at various conditions failed. The structure of the products was established by elemental analyses and IR spectra .

Condensation of **1** with benzaldehyde, p- tolualdehyde and p-anizaldehyde afforded the corresponding Schiff's bases **11a-c**, respectively. The structure of **11a-c** were established by elemental analyses, IR and MS spectra .



a, X = O , R = C_2H_5
b, X = S , R = CH_3
c, X = S , R = C_2H_5
d, X = S , R = C_6H_5
e, X = S , R = COC_6H_5

11 a, Ar = C_6H_5
b, Ar = 4 -CH_3-C_6H_4
c, Ar = 4 -CH_3O-C_6H_4

Chart (1)

The biological activity of the new compounds was evaluated against *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni* parasite in Egypt . The half lethal dose for the new compounds was determined and only compounds **6** and **11a** showed LD_{50} 1 ppm and 10 ppm, respectively and were chosen for further biochemical studies .

EXPERIMENTAL

The melting points are uncorrected . TLC aluminium sheets silica gel 60 F_{245} (Merck) were used for thin layer chromatography . IR spectra were recorded (KBr) on a Perkin-Elmer 1430 spectrophotometer. ^1H NMR were determined in $(CD_3)_2SO$ or $CDCl_3$ with a Varian ^1H Genini 200 spectrometer and chemical shifts were expressed as δ values against $SiMe_4$ as internal standard . ^{13}C NMR spectrum was obtained on a Bruker AC/250 spectrometer . Mass Spectra were recorded on a GCMS-QP 1000 EX Shimadzu .

2-Ethoxymethylene amino-4,5-di(2-furyl)furan-3-carbonitrile 2

A mixture of **1** [7] (2.4 g, 10 m mol), 7 ml triethyl orthoformate and 10 ml acetic anhydride was refluxed for 10 h . The reaction mixture was evaporated, the so formed solid was collected by filtration and crystallized from methanol to give 2.5 g (85 %) of the product (cf. Tables 1&3) .

4-Amino-5,6-di(2-furyl)furo[2,3-d] pyrimidine 3

A stream of ammonia gas was passed in a solution of compound **2** (2.96 g; 10 mmol) in 30 ml methanol at 0 °C for 5.5 h with stirring, then left overnight . The reaction mixture was poured into water . The formed solid was collected by filtration and crystallized to produce 2.37 g of **3** (cf. Tables 1&3) .

4,5-Di(2-furyl)-2-(hydrazinomethylene amino)furan-3-carbonitrile 4

A solution of **2** (2.96 g; 10 mmol) in 20 ml methanol and 2 ml of hydrazine hydrate was heated under reflux for 3 h . The reaction mixture was evaporated . The solid product was collected by filtration and crystallized to yield 1.33 g (cf. Tables 1&3) .

5,6-Di(2-furyl)-4-imino-3H-3-phenylaminofuro[2,3-d]-pyrimidine 5

Equimolar solution of **2** and phenyl hydrazine in methanol was boiled under reflux for 3 h. After evaporation of the solvent, the product was collected and crystallized (cf. Tables 1&3) .

Substituted furo[2,3-d]pyrimidine-4-imine 6 and 7

Equimolar ratio of methyl amine or benzyl amine and **2** in 30ml absolute ethanol were heated under reflux for 10 h, to produce, after evaporation, filtration and crystallization, compounds **6** and 7, respectively (cf. Tables 1&3) .

5,6-Di(2-furyl)-3H-furo[2,3-d] pyrimidine-4-thione 8

A mixture of compound **2** (2.96 g, 10 m mol) and sodium hydrogensulphide (11 m mol) in 20 ml ethanol was refluxed for 6 h . The reaction mixture was poured into water. The solid product, so formed was collected by filtration and crystallized to afford 2.56 g of **8** (cf. Tables 1&3) .

5,6-Di(2-furyl)-1H-3H-3-phenyl-furo[2,3-d]pyrimidine-4-imine-2-one 9

A mixture of compound **1** (2.40 g; 10 mmol) and phenyl isocyanate (1.3 g; 11 mmol) in 50 ml dry ether was refluxed . The solvent was evaporated and the formed solid was collected and crystallized (cf. Tables 2&3) .

Substituted 4,5-di(2-furyl)furan-3-carbonitriles 10a-e

A solution of equimolar amount of compound **1** and ethylisocyanate or substituted isothiocyanates, was boiled under reflux in the proper solvent in unhydrous conditions.The reaction mixture was concentrated and the solid product was collected by filtration to produce the uredo and thiouredo derivatives, respectively (cf. Tables 2&3) .

Substituted 2-aryl-methylene amino-4,5-di(2-furyl)furan-3 carbonitriles 11a-c

A mixture of compound **1** (10 mmol) and (10 mmol) of substituted aldehyde in 25 ml ethanol was boiled under reflux for 6 h. The reaction mixture was then concentrated and the formed solid was collected by filtration and crystallized (cf. Tables 2&3) .

Table 1 : Physical and analytical data for compounds

Compound No.	yield %	m.p °C	cryst. solv.	Mol. Formula Mol. wt.	Analysis calcd/Found(%) C	H	N
2	85	89-91	Methanol	$C_{16}H_{12}N_2O_4$ (296.2)	64.85 64.7	4.08 4.2	9.45 9.2
3	89	193-95	Methanol	$C_{14}H_9N_3O_3$ (267.2)	62.91 62.8	3.39 3.2	15.72 15.7
4	47	136-38	Ethanol	$C_{14}H_{10}N_4O_3$ (282.2)	59.56 59.6	3.57 3.6	19.85 19.7
5	80	158-60	Ethanol	$C_{20}H_{14}N_4O_3$ (358.3)	67.03 66.9	3.93 4.1	15.63 15.3
6	50	120-22	Ethanol	$C_{15}H_{11}N_3O_3$ (281.3)	64.05 64.3	3.94 4.2	14.93 14.7
7	90	125-27	Ethanol	$C_{21}H_{15}N_3O_3$ (357.4)	70.51 70.5	4.20 3.9	11.75 11.47
8	90	171-73	Ethanol	$C_{14}H_8N_2O_3S$ (284.3)	59.14 59.1	2.83 2.6	9.85 9.9

Table 2 : Physical and analytical data and time of reaction .

Compound No.	yield %	m.p °C	cryst. solv.	solvent reflex (hrs)	Mol. Formula Mol. wt.	Analysis calcd/Found (%)		
						C	H	N
9	66	232	Ethanol	Ether 2	$C_{20}H_{13}N_3O_4$ (359.3)	66.8 66.7	3.62 3.5	11.69 11.4
10a	83	174	Ethanol	Ether 2	$C_{16}H_{13}N_3O_4$ (311.3)	61.72 61.9	4.17 4.2	13.49 13.4
10b	61	158	Ethanol	Ether 4	$C_{15}H_{11}N_3O_3S$ (313.3)	57.51 57.0	3.54 3.4	13.42 13.5
10c	83	152	Ethanol	Ether 4	$C_{16}H_{13}N_3O_3S$ (327.3)	58.71 58.9	3.97 4.2	12.84 12.6
10d	64	160	Ethanol	Toluene 10	$C_{20}H_{13}N_3O_3S$ (375.3)	63.98 64.3	3.48 3.6	11.19 11.4
10e	67	156	Ethanol	Xylene 12	$C_{21}H_{13}N_3O_4S$ (403.4)	62.52 62.1	3.25 3.6	10.40 10.0
11a	80	150-52	Dioxane	Ethanol 6	$C_{20}H_{12}N_2O_3$ (328.32)	73.16 72.9	3.68 3.7	8.53 8.4
11b	66	164-66	Methanol	Ethanol 6	$C_{21}H_{14}N_2O_3$ (342.34)	73.67 73.2	4.12 4.4	8.18 8.4
11c	79	165	Methanol	Ethanol 6	$C_{21}H_{14}N_2O_4$ (358.34)	70.38 69.7	3.94 3.7	7.82 7.5

Table 3 : Spectral data for selected compounds

Compound No.	IR cm^{-1}	solvent used	^1H NMR (δ, ppm)	M^+ m/z
2	2228 (CN),	DMSO	1.6(t, 3H, CH_3); 4.35(q, 2H, CH_2); 6.71-7.85(m, 6H, furan protons); 8.70(s, 1H, N=CH).	
3	3340, 3310 (NH_2)			
4	3454, 3300 (NH_2), 3116 (NH), 2202(CN)			
5	3450, 3398, 3304 (NH_2 and NH)	DMSO	6.93(s, br, 1H, NH); 7.05-7.85(m, 11H, aromatic and furan protons); 8.00(s, br, 1H, NH); 8.35(s, 1H, pyrimidine proton)	358
6	3446 (NH), 2962 (CH_3)	CD Cl3	3.31 (s, 3H, CH_3); 6.32(s, br, 1H, NH); 6.55(dd, 2H, furans 4-H); 6.90 (t, 2H, furans 3-H); 7.55(d, 2H, furans 2-H); 8.45(s, 1H, pyrimidine proton).	281
7	3380 (NH), 3060 (CH)ph., 2924(CH_3) aromatic			
8	3448 (NH), 1246 (C=S)	DMSO	6.1-7.8 (m, furan protons and NH); 8.3(d, 1H, pyrimidine proton).	284

Table 3 : Cont.

Compound No.	IR cm^{-1}	solvent used	^1H NMR (δ, ppm)	M$^+$ m/z
9	3436, 3302 (NH), 1746 (CO)			359
10a	3454, 3332 (NH) 1717 (CO), 2200 (CN)			311
10b	3458, 3336 (NH), 2198 (CN)			
10c	3454, 3334 (NH) 2202 (CN)			
10d	3456, 3334 (NH) 2198 (CN)			
10e	3454, 3334 (NH) 2190 (CN)			404
11a	3040, 3010 (CH aromatic) 2226 (CN)			
11b	3080, 3030 (CH aromatic) 2222 (CN)			358
11c	3008, 3029 (CH aromatic) 2228 (CN)			

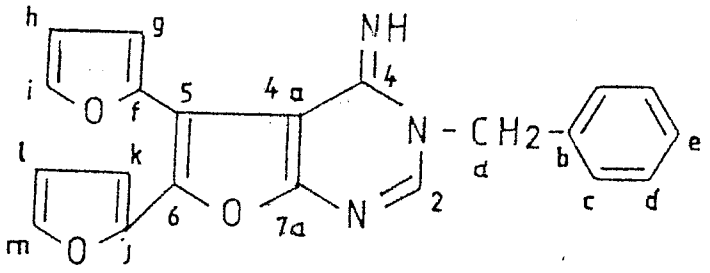


Table 4: ^{13}C NMR (DMSO d $_6$) data of compound 7

C No.	δ ppm	C No.	δ ppm
C_2	154.33	C_e	127.01
C_4	156.79	C_f	143.53
C_{4a}	100.21	C_g	112.10
C_5	104.86	C_h	111.65
C_6	144.72	C_i	139.74
C_{7a}	165.00	C_j	143.74
C_a	44.12	C_k	112.14
C_b	138.74	C_l	111.30
C_c	126.87	C_m	143.24
C_d	128.40		

Determination of the half lethal dose :

The half lethal dose (LD_{50}) for the different compounds was done using 10 *Biomphalaria alexandrina* snails for each concentration . The snails were maintained in the different compounds solutions for 24 hrs.

Table 5 : The molluscicidal activity of the compounds .

Compound No.	LD_{50} (ppm)
1	107
2	40
3	17.5
5	47
6	1
7	160
8	50
9	78
10a	64
10c	25
10e	50
11a	10
11b	50

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تحضير وتفاعلات بعض مركبات الفيوروبيريميدين والمتوقع لها فاعلية بيولوجية

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تم تحضير بعض مشتقات الفيوروبيريميدين بواسطة تفاعل ٢–ايثوكسى ميثيلين أمينو٤–٥ ثنائى(٢ فيوريل) فيوران كربونيتريل مع غاز الأمونيا ، الفينيل هيدرازين ، ميثيل أمين ، بنزيل أمين وكذلك هيدروسلفيد الصوديوم . وقد تم كذلك تفاعل الفيوران اينامينو نيتريل مع بعض مشتقات الأيزوسيانات، الأيزوثيوسيانات، والألدهيدات الأروماتية ليعطى مشتقات الفيوروبيريميدون ، اليوريدو ، الثيويوريدو وقواعد الشيف على التوالى . وقد تم إثبات التركيب الكيميائى للمركبات الناتجة بواسطة التحاليل الدقيقة وطيف الأشعة تحت الحمراء ، والرنين النووى المغناطيسى للبروتونات والكربون – ١٣ وطيف الكتلة . كما تم دراسة النشاط البيولوجى للمركبات .