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Binary heterocyclic systems containing the ethylideneamino linkage: synthesis of some new heterocyclic compounds bearing the naphtho-[2,1-*b*]furan moiety

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Abstract: Ethylidene hydrazine (**4a,b**) and thiazolidin-4-one (**5**) derivatives were synthesized by the reaction of ethylidenethiosemicarbazide derivative (**3a**) with α-haloketone/ethyl bromoacetate, respectively. Hetrocyclization of ethylideneacetohydrazide derivative (**7**) with *o*-phenolic aldehydes gave the corresponding coumarin derivatives (**8,9**). The interaction of **7** with acetylacetone afforded the corresponding pyridine derivative (**10**). Treatment of the arylidene derivative **11b** with malononitrile afforded the corresponding pyran derivative (**12**). The new products **3-12** were subjected to IR, ^{1}H NMR and mass spectra studies.

Keywords: (naphtho-[2,1-*b*]-2-yl)ethylidinehydrazonothiazolidinone, (naphtho[2,1-*b*]furan-2-yl)ethylidenechromene-2-carbohydrazide, 1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitrile.

INTRODUCTION

Naphthofuran derivatives exhibit very potent antibacterial[1–5] and antiparasitic properties[2,3,6,7] but some were shown to be mutagenic in bacteria[8–10] and in mammalian cell systems *in vivo* and *in vitro*.[11–14] Encouraged by these observations, some new naphtho[2,1-*b*]furan derivatives, which might exhibit enhanced antimicrobial activities owing to the incorporation of different pharecophores into their structures, were synthesized.

RESULTS AND DISCUSSION

Condensation of 2-acetylnaphtho[2,1-*b*]furan (**1**)[15] with thiosemicarbazide or thiocarbonohydrazide (**2**) afforded 1-[1-(naphtho[2,1-*b*]furan-2-yl)ethylidene]thiosemicarbazide (**3a**) or 1-[1-(naphtho[2,1-*b*]furan-2-yl)ethylidene]thiocarbono-

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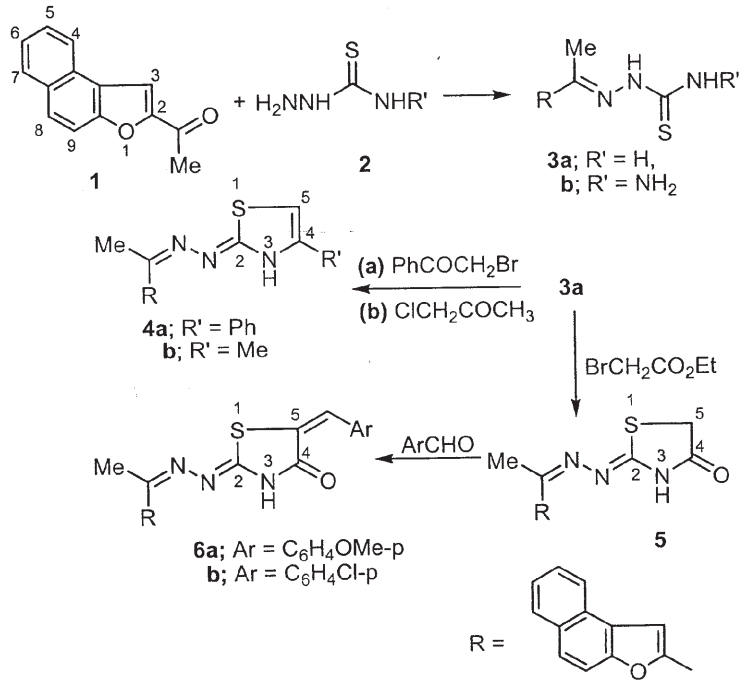
hydrazide (**3b**), respectively. The thiosemicarbazone **3a** was used as the key intermediate in the synthesis of the desired thiazoles *via* their interaction with different α-halocarbonyl derivatives. Thus, the reaction of **3a** with phenacyl bromide and/or chloroacetone in refluxing ethanol in the presence of sodium acetate afforded the thiazole derivatives **4a,b**, respectively, while with ethyl bromoacetate the thiazolidin-4-one **5** was afforded (Scheme 1). Condensation of thiazolidin-4-one **5** with *p*-methoxybenzaldehyde and/or *p*-chlorobenzaldehyde in ethanol containing piperidine as a base gave the arylidene derivatives **6a,b**, respectively (Scheme 1).



Scheme 1.

Structures of **3**, **4**, **5** and **6** were established from their microanalysis and spectral data (Tables I–III). The infrared spectrum of **3a** exhibited absorption at 3576, 3428, 3408, 3212 (NH, NH_2), 1620 (C=N), 1338 (C=S). The ^{1}H NMR spectrum of **3a** in DMSO-d_6 showed signals at δ (ppm): 11.04 (*br*, 1H, NH), 8.84 (*br*, 2H, NH_2), 8.18–7.37 (*m*, 7H, Ar-H, CH-furan), 2.39 (*s*, 3H, Me). The mass spectrum of **3a,b**, **4a**, **5** and **6b** showed molecular ion peaks *m*/*z*: 283 (M^+, 75 %), *m*/*z*: 298 (M^+, 45 %), *m*/*z*: 383 (M^+, 75 %), *m*/*z*: 323 (M^+, 100 %) and *m*/*z*: 445 (M^+, 100 %), respectively.

Condensation of **1** with cyanoacetohydrazide afforded 2-cyano-*N*-[1-(naphtho[2,1-*b*]furan-2-yl)ethylidene]acetohydrazide (**7**) (Scheme 2).

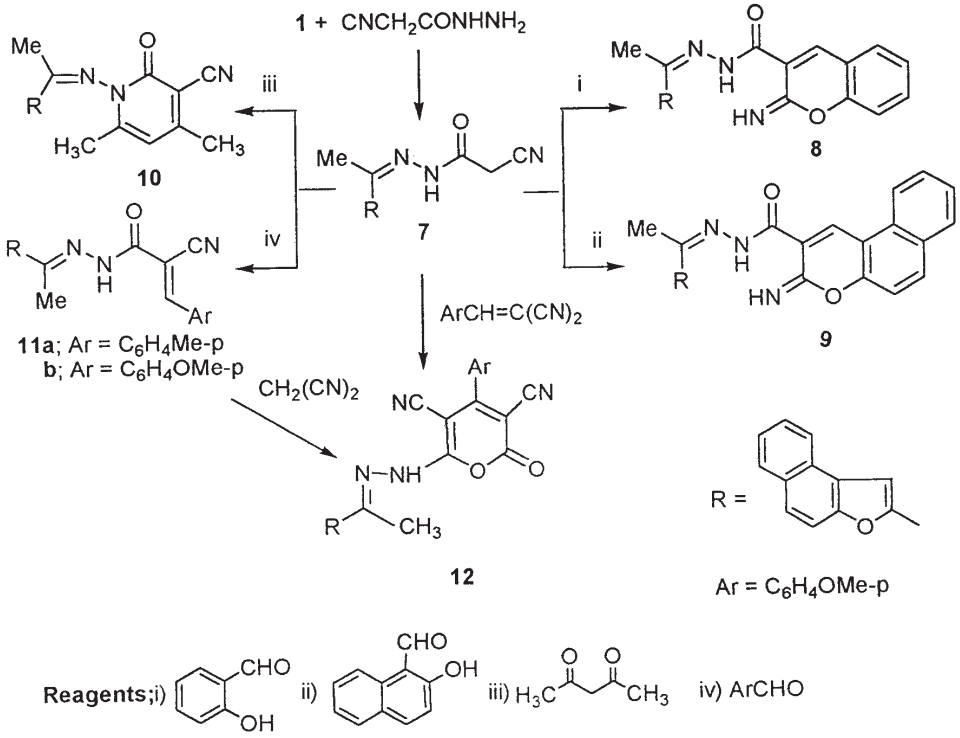
Interaction of **7** with salicylaldehyde or 2-hydroxy-1-naphthaldehyde afforded the chromene derivatives **8** and **9**, respectively, while with acetylacetone the pyridine derivative **10** was obtained (Scheme 2). Condensation of **7** with *p*-tolua-

ldehyde or *p*-anisaldehyde afforded the arylidene derivatives **11a,b**. Reaction of the arylidene derivative **11b** with malononitrile afforded the pyranone derivative **12**. The structure of **12** was further confirmed by independent synthesis *via* direct condensation of **7** with *p*-methoxy-α-cyanocinnamonitrile in refluxing ethanol / piperidine (Scheme 2).

The structrures of **7**, **8**, **9**, **10**, **11** and **6** were established from their microanalysis and spectral data (Tables I–III). The infrared spectrum of **7** exhibited absorption bands at 3248 (NH), 2260 (CN), 1682 (CO). The ^{1}H NMR spectrum of **7** in DMSO-d_6 showed signals at δ (ppm): 11.20 (*br*, 1H, NH), 8.36–7.36 (*m*, 7H, Ar-H, CH-furan), 4.29 (*s*, 2H, CH_2), 2.35 (*s*, 3H, Me). The mass spectrum of **7**, **9**, **10** and **12** showed molecular ion peaks *m*/*z*: 291 (M^+, 100 %), *m*/*z*: 445 (M^+, 16 %), *m*/*z*: 355 (M^+, 65 %) and 474 (M^+, 8 %), respectively.

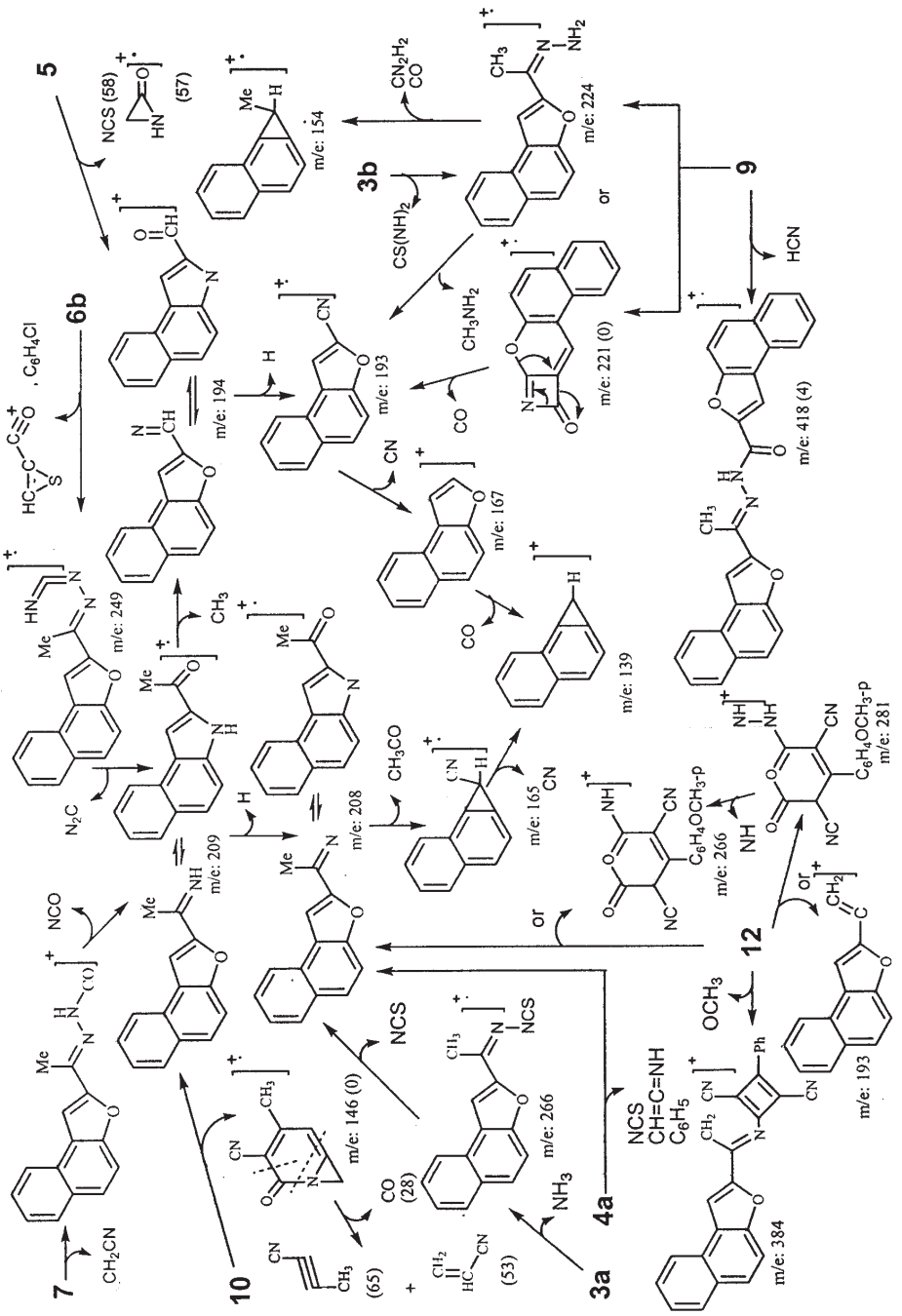
The most important peaks observed in the mass spectra of naphtho[2,1-*b*]furan derivatives **3a–12** are listed in Table I and are arranged in columns according to the presumed composition.

The mass spectra of compounds **5**, **6b** and **7** are characterized by intense molecular ion peaks as the base peak and the other molecular ions were detected in high abundance, except for compounds **9** and **12** which contain chromene and



Scheme 2.

Scheme 3. Proposed fragmentation pathway for the EI spectra of the substituted naphtho[2,1-b]furans **3a-12**.



α-pyran-2-one moieties, respectively, when they were detected in low abundance.

Their high stability is due to the extension of the conjugation of the furan ring to the naphthofuran system. The main fragments were formed by elimination of the side groups attached to the ethylidenamino function to give fragments at *m*/*z*: 209 and 208, followed by successive elimination of CH_3, H, CN and CO to give fragments at *m*/*z*: 194, 193, 167, 165 and 139 (Scheme 3).

BIOLOGICAL ACTIVITIES

The antimicrobial investigations revealed that compound **4a** possesses moderate activity (zone inhibition between 8–12 mm whereas for the standard drug, zone inhibition 12–15 mm) against all the tested microorganisms (Table IV) except fungi (*Candida albicans*, *Aspergillus niger*). On the other hand the remaining compounds exhibited weak or no activity against all the tested organisms.

EXPERIMENTAL

Melting points were measured using a melting point apparatus (Stuart Scientific Co., UK) and remained uncorrected. The IR spectra were recorded on a Shimadzu IR 440 spectrophotometer (Shimadzu, Japan) in KBr. The ^{1}H NMR spectra were measured on a Varian Mercury (300 MHz) spectrometer (Varian, UK), using TMS as the internal standard and DMSO-d_6 as the solvent. Mass spectra were run on a Shimadzu GC-MS QP 1000 EX mass spectrometer. Microanalytical data were obtained from the Microanalytical Unit at Center, Faculty of Science, Cairo Univerisity (Egypt). Spectral and microanalytical data are given in Tables I–III. The paper discs were manufactured by Bristol-Myers Squibb, Giza, Egypt.

Synthesis of 1-[*1-(naphtho*[*2,1-*b]*furan-2-yl)ethylidene*]*thiosemicarbazide (**3a**) and 1-*[*1-(naphtho*[*2,1-*b]*furan-2-yl)ethylidene*]*thiocarbonohydrazide (**3b**)*

A mixture of 2-acetylnaphtho[2,1-*b*]furan (**1**) (0.01 mol) and thiosemicarbazide or thiocarbonohydrazide (**2**) (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The solid which separated on heating was filtered off and recrystallized from the appropriate solvent to give **3a,b**.

*Synthesis of 2-(4-phenyl/or methyl thiazol-2(3*H*)-ylidene)-1-*[*1-(naphtho*[*2,1-*b]*furan-2-yl)ethylidene*]*hydrazine (**4a,b**)*

A mixture of **3a** (0.01 mol) and phenacyl bromide or chloroacetone (0.01 mol) and fused sodium acetate (0.02 mol) in ethanol (40 mL) was refluxed for 2 h. The obtained product was collected by filtration, washed with water and recrystallized from the appropriate solvent to give **4a,b**.

Synthesis of 2-[*1-(naphtho*[*2,1-*b]*furan-2-yl-ethylidene)hydrazono*]*thiazolidin-4-one (**5**)*

A mixture of **3a** (0.01 mol), ethyl bromoacetate (0.01 mol) and fused sodium acetate (0.02 mol) in ethanol (40 mL) was refluxed for 2h. The obtained product was collected by filtration, washed with water and recrystallized from acetic acid to give **5**.

Synhtesis of 5-(4-methyl/or chloro benzylidene)-2-[*(1-(naphtho*[*2,1-*b]*furan-2-yl)ethylidene)hydrazono*]*thiazolidin-4-one (**6a,b**)*

A mixture of **5** (0.01 mol), the appropriate aromatic aldehyde (0.01 mol) in ethanol (30 ml) and a few drops of piperidine was refluxed for 3 h. The solid product was collected by filtration and recrystallized from the appropriate solvent to give **6a,b**.

*Synthesis of 2-cyano-*N*'-*[*1-(naphtho*[*2,1-*b]*furan-2-yl)ethylidene*]*acetohydrazide (7)*

A mixture of **1** (0.01 mol) and cyanoacetohydrazide (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The solid which separated on heating was filtered off and recrystallized from dioxane to give **7**.

TABLE I. Significant peaks in the EI (70 ev) spectra of compounds **3a,b**, **4a**, **5**, **6b**, **7**, **9**, **10** and **12**

Comp. No.	*m/z* (intensity/%)							
	M^+	209	208	194	193	165	139	Other peaks
3a	283 (75)		208 (67)			165 (68)	139 (77)	266 (100), 87 (12), 50 (77)
3b	298 (45)							224 (100), 154 (29), 106 (19), 74 (16)
4a	383 (75)		208 (35)	194 (48)			139 (100)	102 (12), 64 (44)
5	323 (100)			194 (78)		165 (54)	139 (40)	
6b	445 (100)	209 (47)		194 (98)		165 (68)		249 (11), 89 (36)
7	291 (100)	209 (44)				165 (57)		251 (44), 68 (11)
9	445 (16)				193 (93)	165 (66)		418 (4), 224 (100), 112 (9), 63 (21)
10	355 (65)	209 (18)			193 (48)		139 (100)	324 (49), 51 (22)
12	474 (8)		208 (11)	194 (35)	193 (26)	165 (49)	139 (68)	384 (100), 281 (95), 266 (26), 36 (22)

Synthesis of 2-imino-N'-[*1-(naphtho*[*2,1*-b]*furan-2-yl)ethylidene*]-*2*H-*chromene-3-carbohydrazide* ***(8)***

To a mixture of **7** (0.01 mol) and salicylaldehyde (0.01 mol) in ethanol (50 mL), a few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3 h. The solid product was collected by filtration and recrystallized from DMF to give **8**.

Synthesis of 3-imino-N'-[*1-(naphtho*[*2,1*-b]*furan-2-yl)ethylidene*]-*3*H-*benzo*[f] *chromene-2-carbohydrazide* ***(9)***

To a mixture of **7** (0.01 mol) and 2-hydroxy-1-naphthaldehyde (0.01 mol) in ethanol (50 mL), a few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3 h. The isolated product was collected and recrystallized from DMF to give **9**.

Synthesis of 1-[1-(naphtho[2,1-b*]furan-2-yl)ethylideneamino]-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitrile* ***(10)***

To a mixture of **7** (0.01 mol) and acetylacetone (0.01 mol), a few drops of piperidine was added as catalyst. The reaction was fused in oil bath at 150 °C for 1 h. The isolated product was collected and recrystallized from dioxane to give **10**.

Synthesis of 2-cyano-3-(4-substituted phenyl)-N'-*[1-(naphtho[2,1*-b*]furan-2-yl)ethylidene]acrylohydrazide* ***(11a,b)***

A mixture of **3** (0.01 mol), the appropriate aromatic aldehydes (0.01 mol) in ethanol (30 mL) and a few drops of piperidine was refluxed for 3 h. The solid product was collected by filtration and recrystallized from the proper solvent to give **11a,b**.

Synthesis of 6-[2-(1-(naphtho[2,1-b*]furan-2-yl)ethylidene)hydrazino]-4-(4-methoxyphenyl)-2-oxo-2*H-*pyran-3,5-dicarbonitrile* ***(12)***.

Method A. To a mixture of **11b** (0.01 mol) and malononitrile (0.01 mol) in ethanol (50 mL), a few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3 h. The isolated product was collected and recrystallized from DMF to give **12**.

Method B. To a solution of **7** (0.01 mol) and *p*-methoxy-α-cyanocinnamonitrile (0.01 mol) in ethanol (50 mL), a few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3 h. The isolated product was collected and recrystallized from DMF to give **12**; m.p. and mixed m.p determined with an authentic sample gave no depression.

Antibacterial activity

The newly synthesized compounds were screened for their antimicrobial activities *in vitro* against two species of Gram-positive bacteria *Bacillus subtilis* (ATCC 7972) (BS), *Staphylococcus aureus* (NCTC 7447) (SA), two Gram-negative bacteria, *Escherichia coli* (NCTC 10416) (EC), *Pseudomonas aeruginosa* (ATCC 10415) (PA) and two fungi, *Candida albicans* (IMRU 3669) (CA), and *Aspergillus niger* (ATCC 6275) (AN) microorganisms. The activities of these compounds were tested using disc diffusion method.[16,17] The area of zone of inhibition was measured using neomycin (30 mg) as standard antibiotic.

The tested compounds were dissolved in *N,N*-dimethylformamide (DMF) to get a solution of 1 mg mL^{-1}. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28 °C. *N,N*-Dimethylformamide (DMF) showed no inhibition zones. Standard antibiotic neomycin was used as a reference (Table IV).

TABLE II. Physical and analytical data of the newly synthesized compounds (**3-12**)

Comp. No.	Yield/% Color	m.p. °C	Solvent cryst.	Molecular formula (*M*)	Analysis / % Found/calculated		
					C	H	N
3a	70 Brown	230–232	Ethanol	$C_{15}H_{13}N_3OS$ (283.35)	63.50	4.58	14.80
					63.58	4.62	14.83
3b	85 Brown	245–247	Benzene	$C_{15}H_{14}N_4OS$ (298.36)	60.35	4.70	18.70
					60.38	4.73	18.78
4a	65 Black	250–252	Ethanol/Benzene	$C_{23}H_{17}N_3OS$ (383.47)	72.00	4.43	10.92
					72.04	4.47	10.06
4b	70 Black	245–247	Ethanol/Benzene	$C_{18}H_{15}N_3OS$ (321.40)	67.22	4.65	13.00
					67.27	4.70	13.07
5	70 P. yellow	278–280	Acetic acid	$C_{17}H_{13}N_3O_2S$ (323.37)	63.10	4.00	12.90
					63.14	4.05	12.99
6a	83 P. yellow	230–232	Dioxane	$C_{25}H_{19}N_3O_3S$ (441.50)	67.95	4.30	9.50
					68.01	4.34	9.52
6b	85 Yellow	255–257	Dioxane	$C_{24}H_{16}ClN_3O_2S$ (445.92)	64.60	3.60	9.40
					64.64	3.62	9.42
7	85 Yellow	235–237	Dioxane	$C_{17}H_{13}N_3O_2$ (291.30)	70.00	4.45	14.35
					70.09	4.50	14.42
8	82 Yellow	239–241	DMF	$C_{24}H_{17}N_3O_3$ (395.41)	72.85	4.30	10.60
					72.90	4.33	10.63
9	90 Brown	242–244	DMF	$C_{28}H_{19}N_3O_3$ (445.47)	75.45	4.25	9.40
					75.49	4.30	9.43
10	75 Brown	245–247	Dioxane	$C_{22}H_{17}N_3O_2$ (355.39)	74.30	4.75	11.75
					74.35	4.82	11.82
11a	70 Yellow	240–242	Dioxane	$C_{25}H_{19}N_3O_2$ (393.44)	76.25	4.85	10.63
					76.32	4.87	10.68
11b	75 Brown	248–250	Dioxane	$C_{25}H_{19}N_3O_3$ (409.44)	73.30	4.65	10.22
					73.34	4.68	10.26
12	90 Brown	260–262	DMF	$C_{28}H_{18}N_4O_4$ (474.47)	70.00	3.80	11.00
					70.88	3.82	11.81

TABLE III. Spectral data of the prepared compounds

Comp. No	IR (ν, cm^{-1})	^1H NMR
3a	3576, 3428, 3408, 3300, 3212 (NH, NH_2), 1620 (C=N), 1338 (C=S)	11.04 (*brs*, 1H, NH), 8.84 (*brs*, 2H, NH_2), 8.18–7.37 (*m*, 7H, Ar-H+CH-furan), 2.39 (*s*, 3H, Me)
3b	3400, 3375, 3302, 3294 (NH, NH_2), 1654 (C=N), 1362 (C=S)	11.20 (*brs*, 1H, NH, cancelled by D_2O), 10.58 (*brs*, 1H, NH, cancelled by D_2O), 9.66 (*brs*, 2H, NH_2, cancelled by D_2O), 8.33–7.52 (*m*, 7H, Ar-H+CH-furan), 2.37 (s, 6H,2Me)
4a	3205 (NH), 1618 (C=N)	
4b	3372 (NH), 1624 (C=N)	8.35–7.49 (*m*, 7H, Ar-H + CH-furan), 6.55 (*s*, 1H, CH-thiazole), 6.26 (*brs*, 1H, NH), 2.35 (*s*, 3H, Me)
5	3155 (NH), 1704 (CO)	12.05 (*brs*, 1H, NH, cancelled by D_2O), 8.39–7.55 (*m*, 7H, ArH + CH-furan), 3.91 (*s*, 2H, CH_2), 2.43 (*s*, 3H, Me)
6a	3150 (NH), 1700 (CO)	12.50 (*brs*, 1H, NH), 8.21 (*s*, 1H, CH=C), 8.43–7.12 (*m*, 11H, Ar-H + CH-furan), 3.84 (*s*, 3H, OMe), 2.51 (*s*, 3H, Me)
6b	3576, 3428 (NH), 1696 (CO)	
7	3248 (NH), 2260 (CN), 1682 (CO)	11.20 (*brs*, 1H, NH), 8.36–7.36 (*m*, 7H, Ar-H + CH-furan), 4.29 (*s*, 2H, CH_2), 2.35 (*s*, 3H, Me)
8	3300, 3278 (NH), 1678 (CO)	13.67 (*brs*, 1H, NH), 9.29 (*brs*, 1H, NH), 8.60 (*s*, 1H, CH-pyran), 8.33–7.18 (*m*, 11H, Ar-H, CH-furan), 2.38 (*s*, 3H, Me)
9	3432, 3268 (NH), 1676 (CO)	13.73 (*brs*, 1H, NH), 9.29 (*brs*, 1H, NH), 9.17 (*s*, 1H, CH-pyran), 8.49–7.38 (*m*, 13H, Ar-H, CH-furan), 2.40 (*s*, 3H, Me)
10	2216 (CN), 1652 (CO)	8.59–7.60 (*m*, 7H, Ar-H, CH-furan), 6.46 (*s*, 1H, CH-pyridine), 2.37 (*s*, 3H, Me), 2.30 (*s*, 3H, Me), 2.26 (*s,* 3H, Me)
11a	3354 (NH), 2208 (CN), 1688 (CO)	10.51 (*brs*, 1H, NH, cancelled by D_2O), 8.33 (*s*, 1H, CH=C), 8.26–7.41 (*m*, 11H, Ar-H + CH-furan), 2.42 (*s*, 6H, 2Me)
11b	3344 (NH), 2204 (CN), 1682 (CO)	10.46 (*brs*, 1H,NH), 8.36 (*s*, 1H, CH=C), 8.33–7.16 (*m*, 11H, Ar-H + CH-furan), 3.88 (*s*, 3H, OMe), 2.47 (*s*, 3H, Me)
12	3310 (NH), 2206 (CN), 1648 (CO)	8.41–7.06 (*m*, 11H, Ar-H + CH-furan), 5.64 (*brs*, 1H, NH, cancelled by D_2O), 3.83 (*s*, 3H, OMe), 3.34 (*s*, 3H, Me)

TABLE IV. Antibacterial and antifungal activities of the newly synthesized compounds

Comp. No.	Inhibiton zone diameter in mm					
	ATCC-7972	NCTC-7447	NCTC-10416	ATCC-10415	IMRU-3669	ATCC-6275
3a	– ve	– ve	– ve	– ve	– ve	– ve
3b	– ve	– ve	– ve	– ve	– ve	– ve
4a	++ ve	++ ve	++ ve	++ ve	– ve	– ve
4b	– ve	– ve	– ve	– ve	– ve	– ve
5	– ve	– ve	– ve	– ve	– ve	– ve
6a	+ ve	+ ve	+ ve	– ve	– ve	– ve
6b	+ ve	+ ve	+ ve	+ ve	– ve	– ve
7	– ve	– ve	– ve	– ve	– ve	– ve
9	– ve	– ve	– ve	– ve	– ve	– ve
Neomycin (30 mg mL^{-1})	+++ ve	+++ ve	+++ ve	+++ ve	+++ ve	+++ ve

– ve (no inhibition zone), + ve (inhibiton zone up to 8 mm), ++ ve (inhibition between 8–12 mm), +++ ve (inhibition between 12–15 mm).

ИЗВОД

БИНАРНИ ХЕТЕРОЦИКЛИЧНИ СИСТЕМИ СА ЕТИЛИДЕНАМИНСКОМ ВЕЗОМ: СИНТЕЗА НЕКИХ НОВИХ ХЕТЕРОЦИКЛИЧНИХ ЈЕДИЊЕЊА КОЈА САДРЖЕ НАФТО[2,1-*b*]ФУРАНСКЕ СТРУКТУРЕ

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Деривати етилиденхидразина (**4a,b**) и тиазолидин-4-она (**5**) синтетизовани су у реакцији деривата етилидентиосемикарбазида (**3a**) са α-халокетоном односно етилбромоацетатом. Хетроциклизација деривата етилиденацетохидразида (**7**) са *o*-фенолним алдехидима даје одговарајуће кумаринске деривате (**8, 9**). Интеракција **7** са ацетилацетонима дала је одговарајући дериват пиридина (**10**). Третирање арилиден-деривата **11b** са малононитрилом дала је одговарајући дериват пирана (**12**). Структура нових продуката **3-12** проучавана је преко IR, ^{1}H NMR и масених спектара.

(Примљено 7. априла, ревидирано 31. августа 2005)

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