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Antimicrobial Activities of some Synthesized Pyridines, Oxazines and Thiazoles from 3-Aryl-1-(2-naphthyl)prop-2-en-1-ones

Salwa F. MOHAMED * [1], Mohamed M. YOUSSEF [2], Abd El-Galil E. AMR [1], Eman R. KOTB [3]

[1] Applied Organic Chemistry, National Research Center, Dokki, Cairo, Egypt
[2] Chemistry Department, Faculty of Science, Cairo University, Egypt
[3] Photochemistry Department, National Research Center, Dokki, Cairo, Egypt

Abstract

3-Aryl-1-(2-naphthyl)-prop-2-en-1-ones were reacted with ethyl cyanoacetate to produce 4-aryl-6-(2-naphthyl)-2-oxo-1,2-dihydropyridine-3-carbonitriles, which were treated with ethyl chloroacetate to give the corresponding ester. Treatment of the latter ester with hydrazine hydrate or anthranilic acid afforded hydrazides and benzoxazines. The hydrazides were reacted with benzaldehyde or phenylisothiocyanate to afford the corresponding hydrazone and thiosemicarbazide derivatives, which were cyclized with chloroacetic acid or thioglycolic acid to the corresponding thiazole derivatives. 3-Aryl-1-(2-naphthyl)-prop-2-en-1-ones were either condensed with malononitrile under different conditions to produce carbonitrile derivatives or treated with active methylene reagents to afford the substituted cyclohexene derivatives. The structure assignment of the new compounds is based on chemical and spectroscopic evidence. Some of these compounds exhibited antimicrobial activities comparable to Ampicillin® as reference drug.

Keywords

α,β-Unsaturated ketones • Hydrazones • Thiazoles • Benzoxazine • Antimicrobials

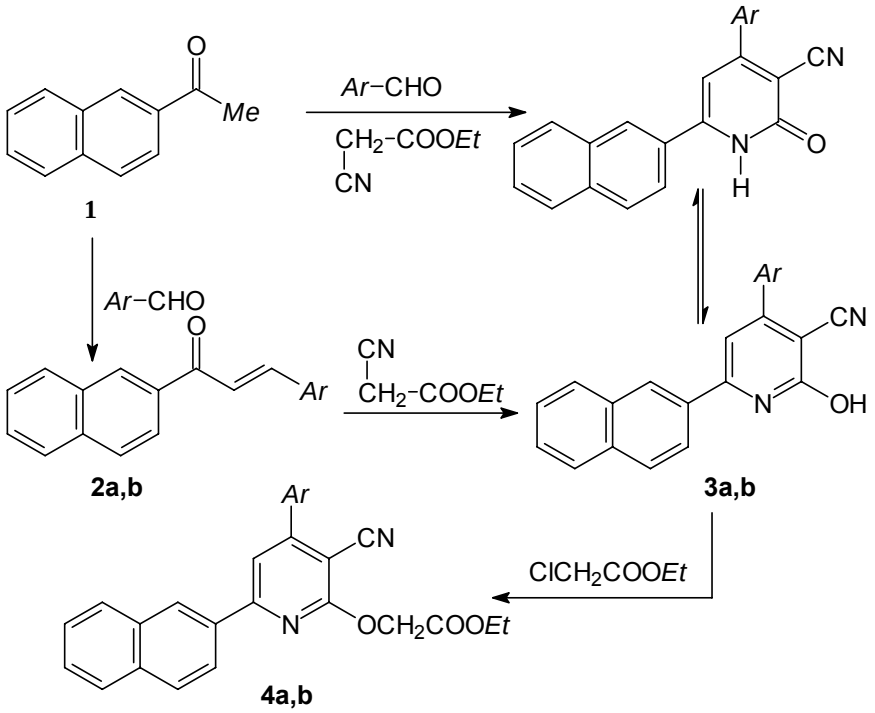
* Corresponding author. Fax.: +202+33370-931.
E-mail: salwa.fahim@hotmail.com (S. F. Mohamed).

Introduction

In previous works we reported that certain substituted pyridines, pyrimidines and their chiral macrocyclic derivatives have antidepressant, antimicrobial, anticancer, analgesic, and anticonvulsant activities [1–7]. α,β-Enones are widely used as versatile precursors for synthesis of several types of heterocyclic compounds, such as isoxazoles [8], thiazoles [9], thiadiazoles [10], oxazolopyridines, pyrans, pyridines and pyrimidines [11, 12], triazines [13], and flavonoids [14]. In view of these observations and as continuation of our previous work in heterocyclic chemistry, we synthesized some new heterocyclic derivatives and tested their antimicrobial activities.

Results and Discussion

Chemistry



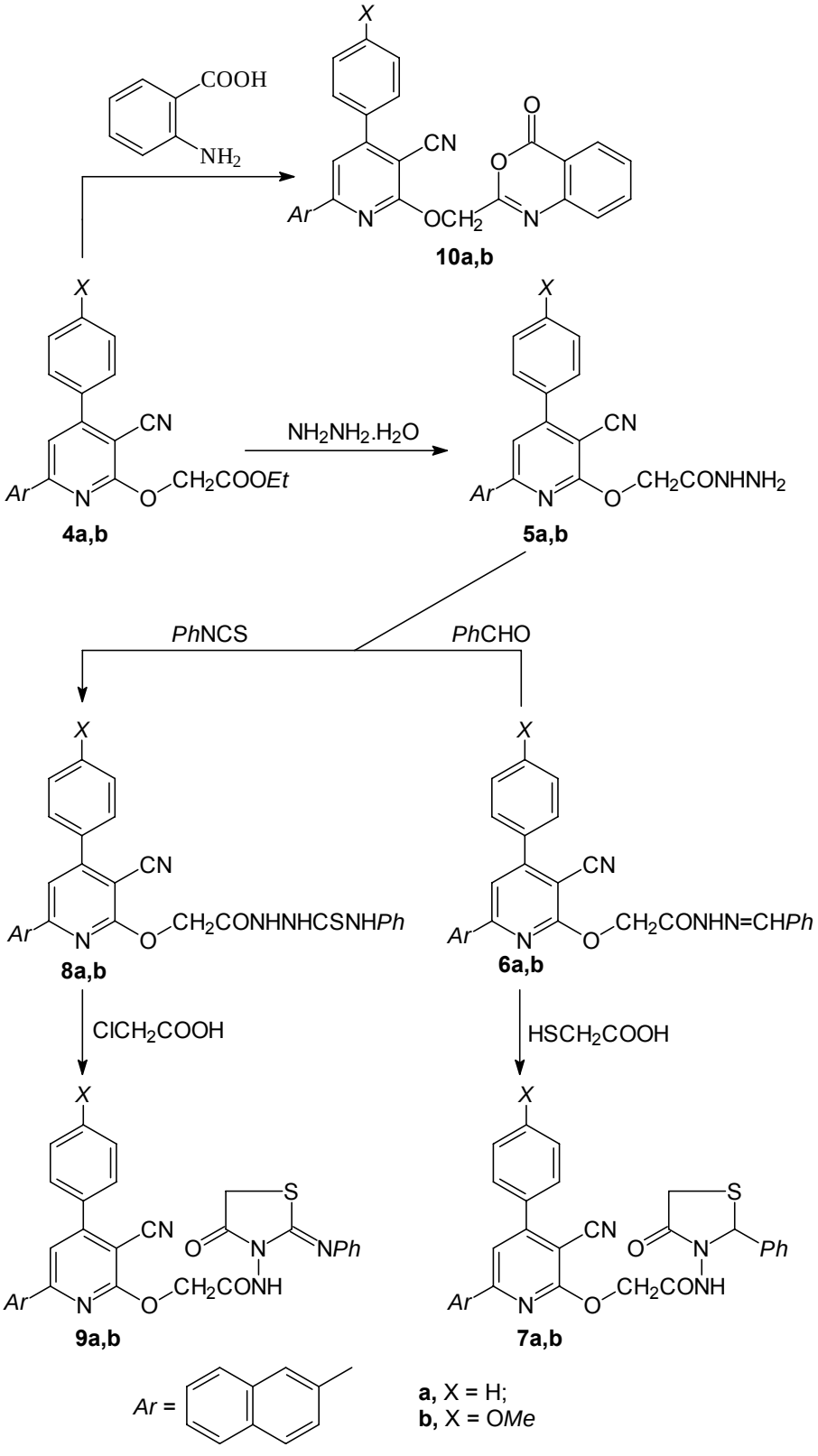
a, *Ar* = *Ph*; **b,** *Ar* = $C_6H_4OMe(p)$

Sch. 1.

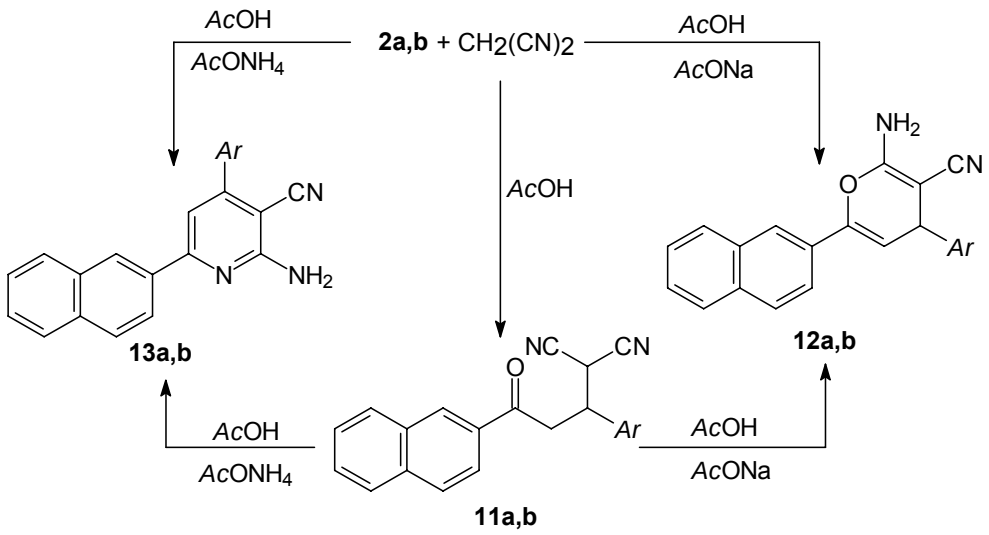
3-Aryl-1-(2-naphthyl)prop-2-en-1-ones (**2a,b**) were reacted with ethyl cyanoacetate in refluxing ethanol in the presence of ammonium acetate to produce dihydropyridinecarbonitriles **3a,b**. One-step synthesis [15] was used to synthesize compounds **3a,b** in good yields by refluxing of 2-acetylnaphthalene, aromatic aldehyde and ethyl cyanoacetate in ethanol containing ammonium acetate as a catalyst. The latter compounds **3a,b** were reacted with ethyl chloroacetate in dry acetone, in the presence of anhydrous potassium carbonate to afford the ethyl glycolate derivatives **4a,b** (Scheme 1).

The esters **4a,b** were reacted with hydrazine hydrate in refluxing ethanol to give the corresponding hydrazides **5a,b**, which were refluxed with benzaldehyde in ethanol to produce the corresponding hydrazone derivatives **6a,b,** followed by cyclization with thioglycollic acid to thiazoles **7a,b**. While, compounds **5a,b** were reacted with phenylisothiocyanate in dry dioxane to obtain thiosemicarbazides **8a,b**, which were cyclized with chloroacetic acid in ethanol to produce 2-*N*-phenylthiazoles **9a,b**. But, compounds **4a,b** were fused with anthranilic acid at 110°C to give oxazinone derivatives (**10a,b**) (Scheme 2).

Condensation of **2a,b** with malononitrile in acetic acid under reflux afforded the oxapentanoic acid nitrile derivatives **11a,b**, which cyclized by refluxing in acetic acid in the presence of anhydrous sodium acetate or ammonium acetate to afford the corresponding cyanoaminopyranes **12a,b** or cyanoaminopyridines **13a,b**, respectively. However, the later compounds **12a,b** and **13a,b** were also prepared directly from the chalcone derivatives **2a,b** by reacting it with malononitrile in acetic acid in the presence of sodium acetate or ammonium acetate (Scheme 3).


COOH
NH2
X
CN
O
Ar
N
OCH2
10a,b
4a,b
NH2NH2.H2O
CH2COOEt
5a,b
CH2CONHNH2
PhNCS
PhCHO
8a,b
CH2CONHNHCSNHPh
6a,b
CH2CONHN=CHPh
ClCH2COOH
HSCH2COOH
9a,b
NPh
CH2CONH
7a,b
Ph
Ar =
a, X = H;
b, X = OMe

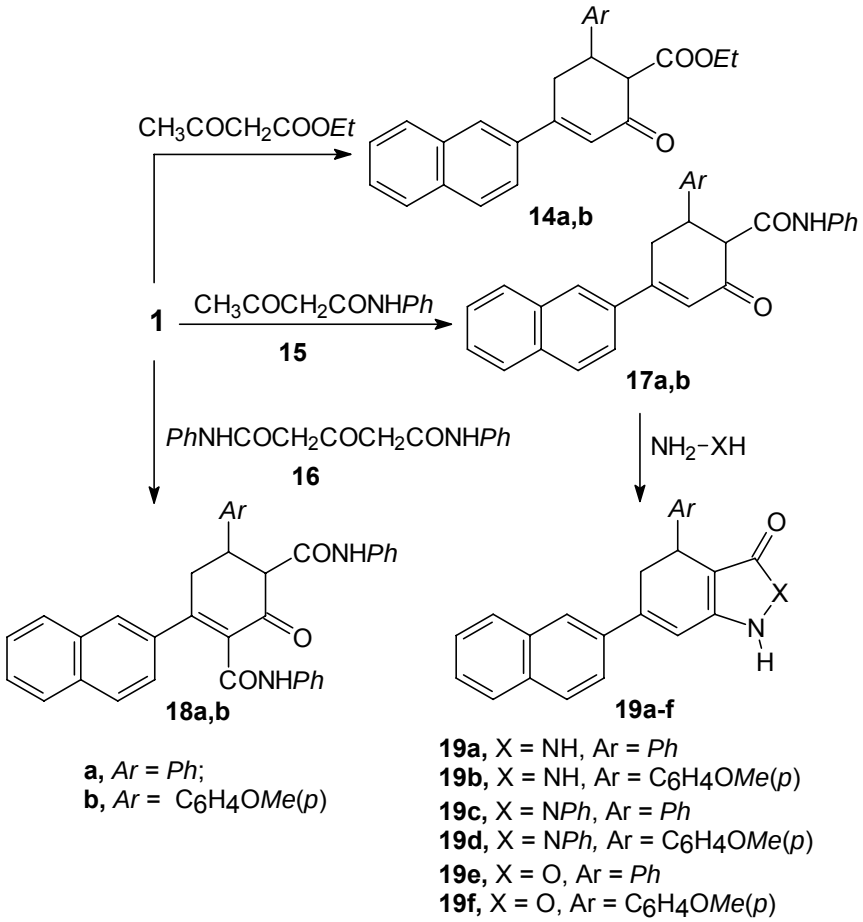
Sch. 2.



a, *Ar* = *Ph*; **b,** *Ar* = $C_6H_4OMe(p)$

Sch. 3.

Moreover, naphthyl chalcones **2a,b** were reacted with ethyl acetoacetate in ethanolic sodium ethoxide solution to give cyclohexenone ethyl esters **14a,b**. While, compounds **2a,b** were reacted with acetoacetanilide (**15**) or acetonedicarboxylic acid dianilide (**16**) in ethanolic sodium hydroxide solution to yield the corresponding cyclohexenone carboxylic acid phenylamides **17a,b** and cylohexenone-1,3-dicarboxilic acid diphenylamides **18a,b**, respectively. Finally, cyclocondensation of **17a,b** with hydrazine hydrate, phenyl hydrazine and hydroxylamine in glacial acetic acid in the presence of sodium acetate afforded the corresponding benzopyrazol-3-ones **19a,b**, 2-phenylbenzopyrazol-3-ones **19c,d** and benzisoxazol-3-ones **19e,f**, respectively (Scheme 4).



Sch. 4.

Antimicrobial evaluation

The newly synthesized heterocyclic compounds, shown in Table 1 were tested for their antimicrobial activity against the following microorganisms: *Escherichia coli, Pseudomonas putide, Bacillus subtilis, Streptococcus lactis, Aspergillus niger, Penicillium sp.* and *Candida albicans*. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The most active compounds were: **5b, 8b** and **17b** and the results are summarized in Table 1.

Tab. 1. Antimicrobial activities of some newly synthesized compounds.

Comp. No.	Inhibition zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E. coli	*P. Putide*	*B. Subtilis*	*S. lactis*	*A. niger*	*P. Sp.*	*C. Albicans*
3a	0	0	0	0	0	0	0
4a	0	0	0	0	0	0	0
5b	12	18	17	17	18	10	0
7b	0	0	0	0	0	0	0
8b	12	10	14	13	8	6	0
11a	0	0	0	0	0	0	0
13b	0	0	0	0	0	0	0
15b	0	0	0	0	0	0	0
17c	20	20	18	18	18	10	13
Chloram-phenicol®	22	21	18	19	20	12	0
Ampicilin®	24	20	19	22	24	14	14

E. coli = Escherichia coli; P. Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Streptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. Albicans = Candida Albicans

The sensitivity of microorganisms to the tested compounds is identified in the following manner *:
Highly sensitive = Inhibition zone 15–20 mm
Moderately sensitive = Inhibition zone: 10–15 mm
Slightly sensitive = Inhibition zone: 5–10 mm
Not sensitive = Inhibition zone: 0 mm
* Each result represents the average of triplicate readings.

Experimental

Chemistry

All melting points are uncorrected and were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accordance with the calculated values) were obtained from the microanalytical unit, Cairo University, Cairo, Egypt. The IR spectra (*KBr*) were recorded on a Pye Unicam SP-1000

spectro-photometer. The ^{1}H-NMR spectra were recorded at a Varian ^{1}H-Gemini 200 Spectro-meter using *TMS* as an internal standard. The mass spectra were performed using GC-MSQP 1000 EX spectrometer (70eV). All reactions were followed by *TLC* (silica gel, aluminum sheets 60 F_{254}, Merck). Compound **2a,b** was prepared from 2-acetyl-naphthalene **1** according to the literature method [16]. Physical and spectral data are shown in Tables 2 and 3.

6-(2-Naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (3a) and 4-(4-Methoxyphenyl)-6-(2-naphthyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3b)

Method A*:* A mixture of **1** (0.17 g, 1 mmol), aromatic aldehyde, namely, benzaldehyde or 4-methoxybenzaldehyde (1 mmol), ethyl cyanoacetate (0.113 g, 1 mmol) and ammonium acetate (0.062 g, 8 mmol) in 40 ml ethanol was heated under reflux for 3 h. The obtained precipitate was filtered off, dried and crystallized from the proper solvent to give compounds **3a,b** (Tables 2 and 3).

Method B. A mixture of **2a,b** (1 mmol), ethyl cyanoacetate (0.113 g, 1 mmole) and ammonium acetate (0.062 g, 8 mmol) in 40 ml ethanol was heated under reflux for 10 h. The obtained precipitate was filtered off, dried and crystallized the proper solvent to give **3a,b** in 56% yield.

Ethyl {[3-cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}acetate (4a) and Ethyl {[3-cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}acetate (4b)

A mixture of **3a,b** (1 mmol), ethyl chloroacetate (0.123 g, 1 mmol) and anhydrous potassium carbonate (0.55 g, 4 mmol) in 30 ml dry acetone was refluxed for 20 h. The reaction mixture was evaporated under reduced pressure, the residue was dissolved in water, the produced was extracted with ether, dried over sodium sulphate anhydrous and filtered off, then evaporated and crystallized the proper solvent to give **4a,b** (Tables 2 and 3).

2-{[3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}acetohydrazide (5a) and 2-{[3-Cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}acetohydrazide (5b)

A solution of **4a,b** (1 mmol) in 50 ml ethanol and 4 ml of hydrazine hydrate (8 mmol) was refluxed for 6 h. After cooling, the separated solid was filtered off, dried and crystallized the proper solvent to give **5a,b** (Tables 2 and 3).

N′*-Benzylidene-2-{[3-cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}acetohydrazide (6a) and* N′*-Benzylidene-2-{[3-cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}acetohydrazide (6b)*

A mixture of **5a,b** (1 mmol) in 30 ml ethanol, three drops of piperidine and benzaldehyde (0.106 g, 1 mmol) was refluxed with stirring for 5 h. After cooling, the formed solid was filtered off and crystallized the proper solvent to give **6a,b** (Tables 2 and 3).

2-{[3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}*-N-*(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide (7a) and 2-{[3-Cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide (7b)

To a stirred solution of **6a,b** (1 mmol) in 30 ml dry benzene, thioglycollic acid (~0.1 g, 1 mmol) in 5 ml dry benzene was added. The reaction mixture was refluxed for 10 h, evaporated under reduced pressure. The residue was solidified with petroleum ether, the obtained solid was filtered off, dried and crystallized the proper solvent to give **7a,b** (Tables 2 and 3).

2-({[3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}acetyl)*-N-*phenylhydrazinecarbothioamide (8a) and 2-({[3-Cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}acetyl)*-N-*phenylhydrazinecarbothioamide(8b)

A mixture of **5a,b** (1 mmol) and phenylisothiocyanate (0.135 g, 1 mmol) in 50 ml dry dioxane was refluxed for 5 h. The reaction mixture was concentrated under

reduced pressure and the obtained solid was filtered off and crystallized the proper solvent to give **8a,b** (Tables 2 and 3).

2-{[3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]oxy}-N-[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]acetamide (9a) and 2-{[3-Cyano-4-(4-methoxyphenyl)-6-(2-naphthyl)pyridin-2-yl]oxy}-N-[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]acetamide (9b)

A mixture of **8a,b** (1 mmol) and chloroacetic acid (~0.1 g, 1 mmol) in 20 ml absolute ethanol was refluxed for 4 h. After cooling, the formed solid was filtered off, dried and crystallized the proper solvent to give **9a,b** (Tables 2 and 3).

6-(2-Naphthyl)-2-[(4-oxo-4H-3,1-benzoxazin-2-yl)methoxy]-4-phenylnicotinonitrile (10a) and 4-(4-Methoxyphenyl)-6-(2-naphthyl)-2-[(4-oxo-4H-3,1-benzoxazin-2-yl)methoxy]nicotinonitrile (10b)

Equimolar amounts of anthranilic acid (0.13 g, 1 mmol) and **4a,b** (1 mmol) were fused at 110°C on an oil bath for 5 h. The reaction mixture was triturated with ethanol, the formed precipitate was filtered off and crystallized the proper solvent to give **10a,b** (Tables 2 and 3).

[3-(2-Naphthyl)-3-oxo-1-phenylpropyl]malononitrile (11a) and [1-(4-Methoxyphenyl)-3-(2-naphthyl)-3-oxopropyl]malononitrile (11b)

A mixture of **2a,b** (1 mole) and malononitrile (~0.1 g, 1 mmol) in 50 ml glacial acetic acid was refluxed for 30 min. After cooling, the reaction mixture was poured onto water with stirring. The formed solid was filtered off, dried and crystallized the proper solvent to give **11a,b** (Tables 2 and 3).

2-Amino-6-(2-naphthyl)-4-phenyl-4H-pyran-3-carbonitrile (12a) and 2-Amino-4-(4-methoxyphenyl)-6-(2-naphthyl)-4H-pyran-3-carbonitrile (12b)
2-Amino-6-(2-naphthyl)-4-phenylnicotinonitrile (13a) and
2-Amino-4-(4-methoxyphenyl)-6-(2-naphthyl)nicotinonitrile (13b)

Method A. A solution of **11a,b** (1 mmol) in 50 ml acetic acid in the presence of 1 g sodium acetate or ~0.1 g ammonium acetate was refluxed for 6 h. The reaction

mixture was poured onto ice-water, the formed solid was filtered off, dried and crystallized the proper solvent to give **12a,b** and **13a,b**, respectively (Tables 2 and 3).

Method B. A mixture of **2a,b** (1 mmol) and malononitrile (~0.1 g, 1 mmol) in 50 ml acetic acid in the presence of 1 g sodium acetate or ~0.1 g ammonium acetate was refluxed for 3 h. The reaction mixture was poured onto ice-water, the formed solid was filtered off, dried and crystallized the proper solvent to give **12a,b** and **13a,b**, respectively (Tables 2 and 3).

Ethyl 4-(2-naphthyl)-2-oxo-6-phenylcyclohex-3-ene-1-carboxylate (14a) and Ethyl 6-(4-methoxyphenyl)-4-(2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate (14b)

To sodium ethoxide solution [prepared by dissolving sodium metal (0.03 g) in 15 ml absolute ethanol], ethyl acetoacetate (0.13 g, 1 mmol) was added and stirred for 1 hr. **2a,b** was added to the reaction mixture and the resulting solution was refluxed for 3 h, after cooling, it was poured onto ice-water and acidified with hydrochloric acid. The product was extracted with ether, washed with water, dried over anhydrous $MgSO_4$, and then evaporated under reduced pressure. The obtained solid was crystallized the proper solvent to give **14a,b** (Tables 2 and 3).

4-(2-Naphthyl)-2-oxo-*N*,6-diphenylcyclohex-3-ene-1-carboxamide (17a) and 6-(4-Methoxyphenyl)-4-(2-naphthyl)-2-oxo-*N*-phenylcyclohex-3-ene-1-carboxamide (17b)

4-(2-Naphthyl)-6-oxo-*N,N'*,2-triphenylcyclohex-4-ene-1,3-dicarboxamide (18a) and 2-(4-Methoxyphenyl)-4-(2-naphthyl)-6-oxo-*N,N'*-diphenylcyclohex-4-ene-1,3-dicarboxamide (18b)

A mixture of **2a,b** (1 mmol) and acetoacetanilide (**15**) (0.18 g, 1 mmol) or acetonedicarboxylic acid dianilide (**16**) (0.3 g, 1 mmol) in 50 ml ethanol containing sodium hydroxide (~0.1 g, 2 mmol) was refluxed for 6 h. The reaction mixture was poured onto acidified ice-water, the formed precipitate was filtered off and

crystallized the proper solvent to give **17a,b** and **18a,b**, respectively (Tables 2 and 3).

6-(2-Naphthyl)-4-phenyl-1,2,4,5-tetrahydro-3H-indazol-3-one (19a) and 4-(4-Methoxyphenyl)-6-(2-naphthyl)-1,2,4,5-tetrahydro-3H-indazol-3-one (19b)

6-(2-Naphthyl)-2,4-diphenyl-1,2,4,5-tetrahydro-3H-indazol-3-one (19c) and 4-(4-Methoxyphenyl)-6-(2-naphthyl)-2-phenyl-1,2,4,5-tetrahydro-3H-indazol-3-one (19d)

6-(2-Naphthyl)-4-phenyl-4,5-dihydro-2,1-benzisoxazol-3(1H)-one (19e) and 4-(4-Methoxyphenyl)-6-(2-naphthyl)-4,5-dihydro-2,1-benzisoxazol-3(1H)-one (19f)

A mixture of **17a,b** (1 mmol) and aminoreagents, namely, hydrazine hydrate, phenyl hydrazine or hydroxylamine hydrochloride (1 mmol) in 30 ml acetic acid containing 2 g of sodium acetate was refluxed for 4 h. The reaction mixture was allowed to cool, poured onto water and the formed solid was filtered off and crystallized the proper solvent to give **19a,b**, **19c,d** and **19e,f**, respectively (Tables 2 and 3).

Tab. 2. Physical properties of the new synthesized compounds

Comp. No.	M.P. (°C) Solvent of cryst.	Yield (%)	Mol. formula (M. wt)	Analysis Calcd (Found)		
				C	H	N
3a	300–301 (AcOH)	80	$C_{22}H_{14}N_2O$ (322.37)	81.97 81.95	4.38 4.33	8.69 8.64
3b	360–361 (AcOH);	72	$C_{23}H_{16}N_2O_2$ (352.39)	78.39 78.34	4.58 4.54	7.95 7.90
4a	165–167 (MeOH)	70	$C_{26}H_{20}N_2O_3$ (408.46)	76.46 76.40	4.94 4.90	6.86 6.80
4b	175–177 (MeOH)	75	$C_{27}H_{22}N_2O_4$ (438.48)	73.96 73.91	5.06 5.00	6.39 6.34
5a	200–201 (MeOH)	70	$C_{24}H_{18}N_4O_2$ (394.43)	73.08 73.02	4.60 4.56	14.20 14.15
5b	205–206 (MeOH)	65	$C_{25}H_{20}N_4O_3$ (424.46)	70.74 70.68	4.75 4.70	13.20 13.15
6a	242–244 (AcOH)	65	$C_{31}H_{22}N_4O_2$ (482.54)	77.16 77.12	4.60 4.55	11.61 11.56
6b	251–252 (AcOH)	62	$C_{32}H_{24}N_4O_3$ (512.57)	74.99 74.94	4.72 4.68	10.93 10.88
7a	225–227 (DMF)	52	$C_{33}H_{24}N_4O_3S$ (556.64)	71.21 71.18	4.35 4.30	10.07 10.00
7b	220–222 (DMF)	55	$C_{34}H_{26}N_4O_4S$ (586.66)	69.61 69.55	4.47 4.42	9.55 9.50
8a	145–146 ($CHCl_3$/pet. ether)	60	$C_{31}H_{23}N_5O_3S$ (545.62)	68.24 68.18	4.25 4.20	12.84 12.78

Tab. 2. (Cont.)

Comp. No.	M.P. (°C) Solvent of cryst.	Yield (%)	Mol. formula (M. wt)	Analysis Calcd (Found)		
				C	H	N
8b	160–162 ($CHCl_3$/pet. ether)	60	$C_{32}H_{25}N_5O_3S$ (559.64)	68.68 68.62	4.50 4.44	12.51 12.46
9a	170–172 ($CHCl_3$/pet. ether)	60	$C_{33}H_{23}N_5O_3S$ (569.64)	69.58 69.52	4.07 4.00	12.29 12.24
9b	210–212 ($CHCl_3$/pet. ether)	60	$C_{34}H_{25}N_5O_4S$ (599.66)	68.10 68.00	4.20 4.14	11.68 11.62
10a	182–184 (EtOH)	60	$C_{31}H_{19}N_3O_3$ (481.51)	77.33 77.28	3.98 3.94	8.73 8.68
10b	195–196 (EtOH)	65	$C_{32}H_{21}N_3O_4$ (511.54)	75.14 75.05	4.14 4.10	8.21 8.16
11a	245–247 (AcOH)	65	$C_{22}H_{16}N_2O$ (324.38)	81.46 81.40	4.97 4.94	8.64 8.60
11b	260–262 (AcOH)	55	$C_{23}H_{18}N_2O_2$ (354.41)	77.95 77.90	5.12 5.05	7.90 7.84
12a	245–247 (AcOH)	65	$C_{22}H_{16}N_2O$ (324.38)	81.46 81.40	4.97 4.92	8.64 8.58
12b	262–263 (AcOH)	60	$C_{23}H_{18}N_2O_2$ (354.41)	77.95 77.90	5.12 5.06	7.90 7.85
13a	230–232 (dioxane)	70	$C_{22}H_{17}N_3$ (323.40)	81.71 81.65	5.30 5.24	12.99 12.95
13b	290–292 (dioxane)	68	$C_{23}H_{19}N_3O$ (353.42)	78.16 78.10	5.42 5.38	11.89 11.84
14a	90–92 (MeOH)	25	$C_{25}H_{22}O_3$ (370.45)	81.06 81.00	5.99 5.94	

Tab. 2. (Cont.)

Comp. No.	M.P. (°C) Solvent of cryst.	Yield (%)	Mol. formula (M. wt)	Analysis Calcd (Found)		
				C	H	N
14b	135–137 (MeOH)	25	$C_{26}H_{24}O_4$ (400.47)	77.98 77.90	6.04 5.98	
17a	220–222 (AcOH)	70	$C_{29}H_{23}NO_2$ (417.51)	83.43 83.36	5.55 5.50	3.35 3.30
17b	230–232 (EtOH)	70	$C_{30}H_{25}NO_3$ (447.53)	80.51 80.46	5.63 5.58	3.13 3.06
18a	240–242 (EtOH)	70	$C_{36}H_{28}N_2O_3$ (536.63)	80.58 80.52	5.26 5.20	5.22 5.18
18b	260–262 (EtOH)	70	$C_{37}H_{30}N_2O_4$ (566.66)	78.43 78.38	5.34 5.28	4.94 4.88
19a	160–162 (dioxane)	65	$C_{23}H_{18}N_2O$ (338.41)	81.63 81.56	5.36 5.30	8.28 8.22
19b	190–192 (dioxane)	60	$C_{24}H_{20}N_2O_2$ (368.44)	78.24 78.20	5.47 5.42	7.60 7.55
19c	220–222 (dioxane)	70	$C_{29}H_{22}N_2O$ (414.51)	84.03 83.98	5.35 5.30	6.76 6.70
19d	255–257 (dioxane)	65	$C_{30}H_{24}N_2O_2$ (444.53)	81.06 80.96	5.44 5.40	6.30 5.96
19e	180–182 (EtOH)	65	$C_{23}H_{17}NO_2$ (339.39)	81.40 81.32	5.05 4.98	4.13 4.05
19f	200–202 (EtOH)	60	$C_{24}H_{19}NO_3$ (369.42)	78.03 77.97	5.18 5.10	3.79 3.72

Tab. 3. Spectral data of newly synthesized compounds

Comp No.	Spectral data		
	IR (ν,cm^{-1})	**MS (m/z, %)**	**^{1}H NMR (DMSO-d$_6$, δ)**
3a	3150 (NH), 2220 (CN), 1650 (CO)	322 [M$^+$, 100].	6.95 (s, 1H, pyrimidine-H5), 7.55-8.50 (m, 12H, Ar-H), 12.85 (bs, 1H, NH, exchangeable with D_2O).
3b	3150 (NH), 2220 (CN), 1658 (CO)	352 [M$^+$, 29], 304 [100].	3.75 (s, 3H, OCH_3), 6.95 (s, 1H, pyrimidine-H5), 7.55-8.50 (m, 12H, Ar-H), 12.90 (bs, 1H, NH, exchangeable with D_2O).
4a	2220 (CN), 1745 (CO)	408 [M$^+$, 4], 332 [100].	1.21 (t, 3H,CH_3), 4.32 (q, 2H, CH_2), 5.20 (s, 2H, CH_2), 7.50-8.65 (m, 13H, Ar-H + pyridine-H5)
4b	2220 (CN), 1745 (CO)	438 [M$^+$, 3], 411 [100].	1.20 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.29 (q, 2H, CH_2), 5.20 (s, 2H, CH_2), 7.15, 7.75 (2d, 4H, Ar-H), 7.90 (s, 1H, pyridine-H5), 8.00-8.90 (m, 7H, Ar-H).
5a	3250, 3160 (NH_2+NH), 2220 (CN), 1675 (CO)	394 [M$^+$, 37], 362 [100].	4.35 (s, 2H, NH_2, exchangeable with D_2O), 5.13 (s, 2H, CH_2), 7.40-8.79 (m, 13H, Ar-H + pyridine-H5), 9.60 (s, 1H, NH, exchangeable with D_2O)
5b	3240, 3155 (NH_2, NH), 2220 (CN), 1675 (CO)	424 [M$^+$, 100].	3.90 (s, 3H, OCH_3), 4.33 (s, 2H, NH_2, exchangeable with D_2O), 5.11 (s, 2H, CH_2), 7.10-8.75 (m, 12H, Ar-H + pyridine-H5), 9.59 (s, 1H, NH, exchangeable with D_2O).
6a	3220 (NH), 2215 (CN), 1670 (CO)	482 [M$^+$, 100].	5.22 (s, 2H, CH_2), 7.40-8.55 (m, 19H, Ar-H + pyridine-H5 + benzylidene-H), 12.93 (s, 1H, NH, exchangeable with D_2O).

Tab. 3. (Cont.)

Comp. No.	Spectral data		
	IR (ν, cm^{-1})	**MS (m/z, %)**	**^{1}H NMR (DMSO-d_6, δ)**
6b	3220 (NH), 2220 (CN), 1675 (CO)	512 [M^+, 4], 372 [100].	3.90 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 7.25-8.59 (m, 18H, Ar-H+ pyridine-H5 + benzylidene-H), 12.95 (s, 1H, NH, exchangeable with D_2O).
7a	3225 (NH), 2220 (CN), 1730,1685 (2CO)	556 [M^+, 18], 451 [100].	3.75 (d, 1H, thiazolidine-H5), 3.95 (d, 1H, thiazolidine-H5), 5.13, 5.21 (2d, 2H, 2 methylene-H), 5.73 (s, 1H, thiazolidine-H2), 7.25-8.75 (m, 18H, Ar-H + pyridine-H5), 10.66 (s, 1H, NH, exchangeable with D_2O).
7b	3225 (NH), 2220 (CN), 1730,1685 (2CO)	586 [M^+, 2], 402 [100].	3.75, 3.95 (2d, 2H, 2 thiazolidine-H5), 3.90 (s, 3H, OCH_3), 5.15, 5.20 (2d, 2H, 2 methylene-H), 5.75 (s, 1H, thiazolidine-H2), 7.25-8.75 (m, 17H, Ar-H + pyridine-H5), 10.69 (s, 1H, NH, exchangeable with D_2O).
8a	3330,3200 (NH), 2220 (CN), 1680 (CO)	529 [M^+, 5], 386 [100].	5.10 (s, 2H, CH_2), 7.10-8.30 (m, 13H, 12 Ar-H + pyridine-H5), 9.20, 9.42, 9.81 (3s, 3H, 3NH, exchangeable with D_2O).
8b	3330,3200 (NH), 2220 (CN), 1685 (CO)	559 [M^+, 5], 520 [100].	3.91 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2), 7.00-8.10 (m, 12H, Ar-H +pyridine-H5), 9.20, 9.40, 9.80 (3s, 3H, 3NH, exchangeable with D_2O).

Tab. 3. (Cont.)

Comp. No.	Spectral data		
	IR (ν, cm^{-1})	**MS (m/z, %)**	**^{1}H NMR (DMSO-d_6, δ)**
9a	3300,3200 (NH), 2220 (CN), 1720,1685 (2CO)	569 [M^+, 3], 386 [100].	3.52 (s, 2H, CH_2 thiazolidine), 5.41, 5.71 (2d, 2H, 2 methylene-H), 7.20-8.80 (m, 18H, Ar-H + pyridine-H5), 9.50 (s, 1H, NH, exchangeable with D_2O).
9b	3300, 3200 (NH), 2220 (CN), 1725, 1685 (2CO	599 [M^+, 3], 465 [100].	3.50 (s, 2H, CH_2 thiazolidine), 3.90 (s, 3H, OCH_3), 5.40, 5.70 (2d, 2H, 2 methylene-H), 7.00-8.50 (m, 17H, Ar-H + pyridine-H5), 9.50 (s, 1H, NH, exchangeable with D_2O).
10a	2220 (CN), 1725 (CO)	481 [M^+, 22], 288 [100].	5.30 (s, 2H, CH_2), 7.10-8.35 (m, 17H, Ar-H + pyridine-H5).
10b	2220 (CN), 1725 (CO)	511 [M^+, 20], 480 [100].	3.61 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.90-8.10 (m, 16H, Ar-H + pyridine-H5)
11a	2210 (CN), 1680 (CO)	324 [M^+, 20], 318 [100].	3.10 (m, 1H, H3), 4.20 (dd, 1H, H4), 4.40 (dd, 1H, H4), 5.10 (d, 1H, H2), 7.00-8.10 (m, 12H, Ar-H).
11b	2210 (CN), 1680 (CO)	354 [M^+, 20], 349 [100].	3.10 (m, 1H, H3), 3.76 (s, 3H, OCH_3), 4.21 (dd, 1H, H4), 4.32 (dd, 1H, H4), 5.15 (d, 1H, H2), 6.88-8.00 (m, 11H, Ar-H).

Tab. 3. (Cont.)

Comp. No.	Spectral data		
	IR (ν, cm^{-1})	**MS (m/z, %)**	**^{1}H NMR (DMSO-d_6, δ)**
12a	3450, 3240 (NH_2), 2180 (CN)	324 [M^+, 77], 300 [100].	2.50 (d, 1H, pyran-H4), 5.00 (s, 2H, NH_2, exchangeable with D_2O), 7.20-8.35 (m, 13H, Ar-H + pyran-H5).
12b	3455,3245 (NH_2), 2190 (CN)	354 [M^+, 75], 425 [100].	2.50 (d, 1H, pyran-H4), 3.80 (s, 3H, OCH_3), 5.00 (s, 2H, NH_2, exchangeable with D_2O), 7.00-8.08 (m, 12H, Ar-H + pyran-H5).
13a	3420,3250 (NH, NH_2), 2190 (CN)	323 [M^+, 100].	2.60 (d, 1H, pyridine-H4), 4.12 (s, 2H, NH_2, exchangeable with D_2O), 7.35-8.50 (m, 13H, Ar-H + pyridine-H5), 12.85 (s, 1H, NH, exchangeable with D_2O).
13b	3420,3245 (NH, NH_2), 2200 (CN)	353 [M^+, 100].	2.60 (d, 1H, pyridine-H4), 3.80 (s, 3H, OCH_3), 4.10 (s, 2H, NH_2, exchangeable with D_2O), 7.20-8.30 (m, 12H, Ar-H + pyridine-H5), 12.80 (s, 1H, NH, exchangeable with D_2O).
14a	1720, 1670 (2CO)	370 [M^+, 100].	1.10 (t, 3H, CH_3), 3.33 (d, 2H, cyclohexene-H5), 3.70 (m, 1H, cyclohexene-H6), 3.90 (q, 2H, CH_2), 4.20 (d, 1H, cyclohexene-H1), 6.80 (s, 1H, cyclohexene-H3), 7.20-8.50 (m, 12H, Ar-H).
14b	1720, 1670 (2CO)	400 [M^+, 100].	1.01 (t, 3H, CH_3), 3.35 (d, 2H, cyclohexene-H5), 3.70 (m, 1H, cyclohexene-H6), 3.76 (s, 3H, OCH_3), 3.90 (q, 2H, CH_2), 4.20 (d, 1H, cyclohexene-H1), 6.80 (s, 1H, cyclohexene-H3), 7.00-8.10 (m, 11H, Ar-H);

Tab. 3. (Cont.)

Comp. No.	Spectral data		
	IR (ν, cm^{-1})	**MS (m/z, %)**	**^1H NMR (DMSO-d_6, δ)**
17a	3260 (NH), 1740, 1640 (2CO)	417 [M^+, 100].	3.20 (d, 2H, CH_2), 3.90 (m, 1H, cyclohexene-H6), 4.00 (d, 1H, cyclohexene-H1), 6.50 (s, 1H, cyclohexene-H3), 7.10-8.35 (m,17H,Ar-H), 10.15 (s,1H,NH, exchange-able with D_2O).
17b	3260 (NH), 1740,1645 (2CO)	447 [M^+, 100].	3.20 (d, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.90 (m, 1H, cyclohexene-H6), 4.00 (d, 1H, cyclohexene-H1), 6.50 (s, 1H, cyclohexene-H3), 6.90-8.00 (m, 17H, Ar-H), 10.10 (s, 1H, NH, exchangeable with D_2O).
18a	3300-3200 (NH), 1710,1680, 1645(3CO)	536 [M^+, 100].	3.05 (d, 2H, CH_2), 4.10 (m, 1H, cyclohexene-H4), 4.50 (d, 1H, cyclohexene-H3), 6.75-8.25 (m, 22H, Ar-H), 10.10, 10.30 (2s, 2H, 2NH, exchangeable with D_2O).
18b	3310-3200 (NH), 1720,1685, 1650(3CO)	566 [M^+, 100]	3.05 (d, 2H, CH_2), 3.75 (s, 3H, CH_3), 4.10 (m, 1H, cyclohexene-H4), 4.50 (d, 1H, cyclohexene-H3), 6.67-8.15 (m, 22H, Ar-H), 10.10, 10.30 (2s, 2H, 2NH, exchangeable with D_2O).
19a	3420 (NH), 1700 (CO)	338 [M^+, 100]	3.00 (d, 2H, CH_2), 4.25 (t, 1H, cyclohexadiene-H4), 7.00-8.10 (m, 13H, Ar-H+ cyclohexadiene-H7), 11.00, 11.30 (2s, 2H, 2NH, exchangeable with D_2O).

Tab. 3. (Cont.)

Comp. No.	Spectral data		
	IR (ν, cm^{-1})	**MS (m/z, %)**	**^{1}H NMR (DMSO-d_6, δ)**
19b	3420 (NH), 1700 (CO)	368 [M^+, 100]	3.00 (d, 2H, CH_2), 3.60 (s, 3H, OCH_3), 4.25 (t, 1H, cyclo-hexadiene-H4), 6.90-8.00 (m, 12H, Ar-H + cyclo-hexadiene-H7), 11.00,11.30 (2s, 2H, 2NH, exchangeable with D_2O).
19c	3400 (NH), 1705 (CO)	414 [M^+, 100]	3.10 (d, 2H, CH_2), 4.40 (t, 1H, cyclohexadiene-H4), 7.00-8.10 (m, 18H, Ar-H + cyclohexadiene-H7), 11.40 (s, 1H, NH, exchangeable with D_2O).
19d	3440 (NH), 1710 (CO)	444 [M^+, 100]	3.10 (d, 2H, CH_2), 3.60 (s, 3H, OCH_3), 4.40 (t, 1H, cyclohexadiene-H4), 6.70-8.00 (m, 17H, Ar-H + cyclohexadiene-H7), 11.40 (s, 1H, NH, exchangeable with D_2O).
19e	3400 (NH), 1710 (CO)	339 [M^+, 100]	3.00 (d, 2H, CH_2), 4.25 (t, 1H, cyclohexadiene-H4), 7.00-8.10 (m, 13H, Ar-H + cyclohexadiene-H7), 11.40 (s, 1H, NH, exchangeable with D_2O).
19f	3400 (NH), 1710 (CO)	369 [M^+, 100].	3.00 (d, 2H, CH_2), 3.60 (s, 3H, OCH_3), 4.30 (t, 1H, cyclohexadiene-H4), 6.90-8.00 (m, 12H, Ar-H + cyclohexadiene-H7), 11.40 (s, 1H, NH, exchangeable with D_2O).

Antimicrobial screening

The newly synthesized heterocyclic compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: *Escherichia coli* and *Pseudomonas putide;* (b) Gram-positive: *Bacillus subtilis* and *Streptococcus lactis;* (c) Fungi: *Aspergillus niger* and *Penicillium sp.;* (d) Yeast: *Candida albicans*

Mediums: Three types of specific media were used in this study:

Medium (1): For bacteria (Nutrient Medium), consisting of (g/l distilled water): peptone, 5 and meat extract, 3. pH was adjusted to 7.0.

Medium 2: For fungi (Potato Dextrose Medium), consisting of (g/l distilled water): Infusion from potatoes, 4 and D(+)glucose, 20. pH was adjusted to 5.5.

Medium 3: For yeast (Universal Medium), consisting of (g/l distilled water): yeast extract, 3; malt extract, 3; peptone, 5 and glucose, 10. pH was adjusted to 5.5.

For solid media, 2% agar was added. All media were sterilized at 121°C for 20 minutes.

Procedure (Filter paper diffusion method) [17]

Proper concentrations of microbial suspensions were prepared from 1 (for bacteria to 3 (for yeast and fungi)-day-old liquid stock cultures incubated on a rotary shaker (100 rbm). In the case of fungi, 5 sterile glass beads were added to each culture flask. The mycelia were then subdivided by mechanical stirring at speed N^{o}. 1 for 30 minutes. Turbidity of microorganisms was adjusted with a spectro-photometer at 350 nm to give an optical density of 1.0. Appropriate agar plates were aseptically surface inoculated uniformly by a standard volume (ca. 1 ml) of the microbial broth culture of the tested microorganism, namely *E. coli, P. putide, B. subtilis, S. Lactis. A. Niger, Penicillium sp. And C. albicans.*

Whatman N^{o}. 3 filter paper discs of 10 mm diameter were sterilized by autoclaving for 15 minutes at 121°C. Test compounds were dissolved in 80% ethyl alcohol to give final concentration of 5 μg/ml. The sterile discs were impregnated with the test compounds (5 μg/disc). After the impregnated discs have been air dried, they were placed on the agar surface previously seeded with the organism to be tested. Discs were gently pressed with forceps to insure thorough contact with the media. Three discs were arranged per dish, suitably spaced apart, i.e. the discs should be separated by a distance that is equal to or slightly greater than the sum of the diameters of inhibition produced by each disc alone. Each test compound was conducted in triplicate. Plates were kept in the refrigerator at 5°C for 1 hour to permit good diffusion before transferring them to an incubator at 37°C for 24 hours for bacteria and at 30°C for 72 hours for yeast and fungi.

Conclusion

In order to reveal a potential activity of nine newly obtained compounds, they were tested on seven bacterial species: Escherichia coli, Pseudomonas putide, Bacillus subtilis, Streptococcus lactis, Aspergillus niger, Penicillium sp., Candida albicans. The obtained results are shown in Table 1. Many of the investigated derivatives presented interesting antibacterial activity.

References

[1] Abdel-Latif NA.
Synthesis and antidepressant activity of some new coumarin derivatives.
Sci Pharm. 2005; 74: 193–216.

[2] Amr AE, Abdel-Latif NA, Abdalla MM.
Synthesis of some new testosterone derivatives fused with substituted pyrazoline ring as 5α-reductase inhibitors.
Acta Pharm. 2006; 56: 203–218.

[3] Amr AE, Abdel-Latif NA, Abdalla MM.
Synthesis and antiandrogenic activity of some new 3-substituted androstano[17,16-c]-5`-aryl-pyrazoline and their derivatives.
Bioorg Med Chem. 2006; 14: 373–384.
[doi:10.1016/j.bmc.2005.08.024]

[4] Amr AE.
Synthesis of some new linear and chiral macrocyclic pyridine carbazides as analgesic and anticonvulsant agents.
Z Naturforsch. 2005; 60b: 990–998.

[5] Amr AE, Sayed HH, Abdulla MM.
Synthesis and reactions of some new substituted pyridine and pyrimidine derivatives as analgesic, anticonvulsant and antiparkinsonian agents.
Arch Pharm Chem Life Sci. 2005; 338: 433–440.
[doi:10.1002/ardp.200500982]

[6] Abo-Ghalia MH, Amr AE.
Synthesis and investigation of a new cyclo-(Nα-dipicolinoyl)pentapeptide of a breast and CNS cytotoxic activity and an ionophoric specifity.
Amino Acids. 2004; 26: 283–289.
[doi:10.1007/s00726-003-0042-8]

[7] Hammam AG, Fahmy AF, Amr AE, Mohamed AM.
Synthesis of novel tricyclic heterocyclic compounds as potential anticancer agents using chromanone and thiochromanone as synthons.
Ind J Chem. 2003; 42B: 1985–1993.

[8] Lakhvich FA, Koroleva EV, Akhrem AA.
Synthesis, chemical transformation, and application of isoxazole derivatives in the total chemical synthesis of natural compounds.
Chem Heterocycl Comp. 1989; 25: 359–375.
[doi:10.1007/BF00480746]

[9] Mukhtar S, Ramadan M, Ansari W, Lemiere G, De Groot A, Dommisse R.
Bifunctional derivative of p,p`-dichlorochalcone Part II. Synthesis of a novel compound 2-[2-carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone.
Molecules. 1999; 4: 232–237.

[10] Bae SH, Kim KS, Park Y.
Reactions of Tetrasulfur Tetranitride Antimony Pentachloride Complex (S4N4•SbCl5) with Primary β-Enaminones and β-Enamino Esters: Synthesis of 4-Substituted 3-Aroyl- and 3-Ethoxycarbonyl-1,2,5-thiadiazoles.
Heterocycles. 2000; 53: 159–172.

[11] Swellem RH, Allam YA, Nawwar GA.
Synthesis of 3-Phenylisoxazolo[3,4-a]carbazoles.
Z Naturforsch. 1999; 54b: 1197–2201.

[12] Bakhite EA.
Convenient heterocyclization reactions with 2-functionalized 3-amino-4-aryl-5,6,7,8-tetrahydrothieno[2,3-b]quinolines: Synthesis of new thienoquinolines, pyridothienoquinolines, pyranothienoquinolines and pyrimidothienoquinolines.
J Chem Res Synop. 2000; 11: 500–501.

[13] Al-Shikh MA, El-Din AMS, Hafez EA, Elnagdi MH.
α-Enones in heterocyclic synthesis, part I. Classical synthetic and environmentally friendly synthetic approaches to alkyl and acyl azoles and azines.
J Chem Res. 2004; 174–179.

[14] Lim SS, Jung SH, Ji J, Shin KH, Keum SR.
Synthesis of flavonoids and their effects on aldose reductase and sorbitol accumulation in streptozotocin-induced diabetic rat tissues.
J Pharm Pharmacol. 2001; 53: 653–668.
[doi:10.1211/0022357011775983]

[15] Nehad AA, Amr EA, Alhusien AI.
Synthesis, reactions and pharmacological screening of heterocyclic derivatives Using nicotinic acid as a natural synthon.
Monatsh Chem. 2007; 138: 559–567.
[doi:10.1007/s00706-007-0628-z]

[16] Attia A, Abdel-Salam OI, Abo-Ghalia MH, Amr EA.
Chemical and biological reactivity of newly synthesized 2-chloro-6-ethoxy-4-acetylpyridine.
Egypt J Chem. 1995; 38: 543–553.

[17] Coffen DL, Korzan DG.
Synthetic quinine analogs. III. Frangomeric and anchimeric processes in the preparation and reactions of α,β-epoxy ketones.
J Org Chem. 1971; 36: 390–395.
[doi:10.1021/jo00802a006]

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