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Activated nitriles in heterocyclic synthesis: Synthesis of new [1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine and [1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine derivatives with promising antibacterial activity

ASHRAF H. F. ABD EL-WAHAB

Department of Chemistry
Faculty of Science
Al-Azhar University
Nasr City 11884 Cairo, Egypt

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2-Amino-5-oxo-pyrano[3,2-c]benzopyran-3-carbonitrile derivative (**3**) was used as precursor for the synthesis of novel benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidines (**4, 6, 7** and **10**), benzopyrano[3',4':5,6] pyrano[3,2-e]-[1,2,4]triazolo[1,5-c]pyrimidines (**9, 11** and **15**), and two 2-amino derivatives of pyrano[3,2-c][1]benzopyrans (**5, 8**). The antibacterial screening for new products was performed.

Keywords: pyrano[3,2-c]benzopyrans, pyrano[2,3-d]pyrimidines, [1,2,4]triazolo[1,5-c]pyrimidines, antibacterial activity

Several derivatives of the pyran or fused 4*H*-pyran ring systems are endowed with different types of biological activitiy. It has been reported that 4*H*-pyran derivatives exhibit antimicrobial activity (1–4), growth stimulating effect (5), antifungal and plant growth regulation effects (6), antitumor activity (7), central nervous system activity (8) and hypotensive effect (9). Moreover, pyran derivatives are well known for their antihistaminic activity (10), platelet antiaggregating activity, local anaesthetic activity (11–13) and inhibiting of influenza virus sialidases (14, 15). They can also act as antiviral agents (16), sex-pheromones (17, 18), anti-allergic agents (19), antiproliferation agents (20, 21), and show kojic amine antinociceptive profile (22), and cardiovascular effect (23). With this in mind and in continuation of our previous work (1–3, 24, 25) using 2-amino-5--oxo-4-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-c][1]benzopyran-3-carbonitrile as starting material, a variety of new [1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidines and [1]benzopyrano-[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines were synthesized and examined for their antibacterial activity.

* Correspondence ash-abdelwabah@hotmail.com

EXPERIMENTAL

Melting points were measured by 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. ^{1}H NMR spectra were measured on a Varian Mercury (300 MHz) spectrometer (Varian, UK), using tetramethylsilane (TMS) as the internal standard, and $CDCl_3$ and DMSO-d_6 as solvents. Mass spectra were run on a Shimadzu GC-MS QP 1000 EX spectrometer. Microanalytical data were obtained from Microanalytical Unit at Cairo University (Egypt) (Table I). Paper discs manufactured by Bristol-Myers Squibb (Egypt) were used.

*Pyranopyrimidine derivatives (**4a, b**). General Procedure*

A mixture of **3** (0.01 mol) in acetic anhydride or benzoyl chloride (30 mL) was heated under reflux for 6 h. The solid product was collected by filtration (Scheme 1). 10-Methyl-7-(*p*-tolyl)-6*H*,7*H*,8*H*-8,9-dihydro-[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8--dione (**4a**) (m.p. > 360 °C, yield 70%) and 10-phenyl-7-(*p*-tolyl)-6*H*,7*H*,8*H*-8,9-dihydro-[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8-dione (**4b**) (m.p. 320 °C, yield 81%) were obtained as colourless crystals from DMF.

*2-Ethoxymethyleneamino-5-oxo-4-(*p*-tolyl)-4*H,5H*-pyrano[3,2-c][1]benzopyran-3--carbonitrile (**5**)*

A mixture of **3** (0.01 mol) and triethyl orthoformate (2 mL) in acetic anhydride (10 mL) was refluxed for 2 h. After cooling, the precipitated product was filtered and washed several times with cold ethanol to give **5** (Scheme 1) as colourless crystals (benzene, m.p. 225 °C, yield 75%).

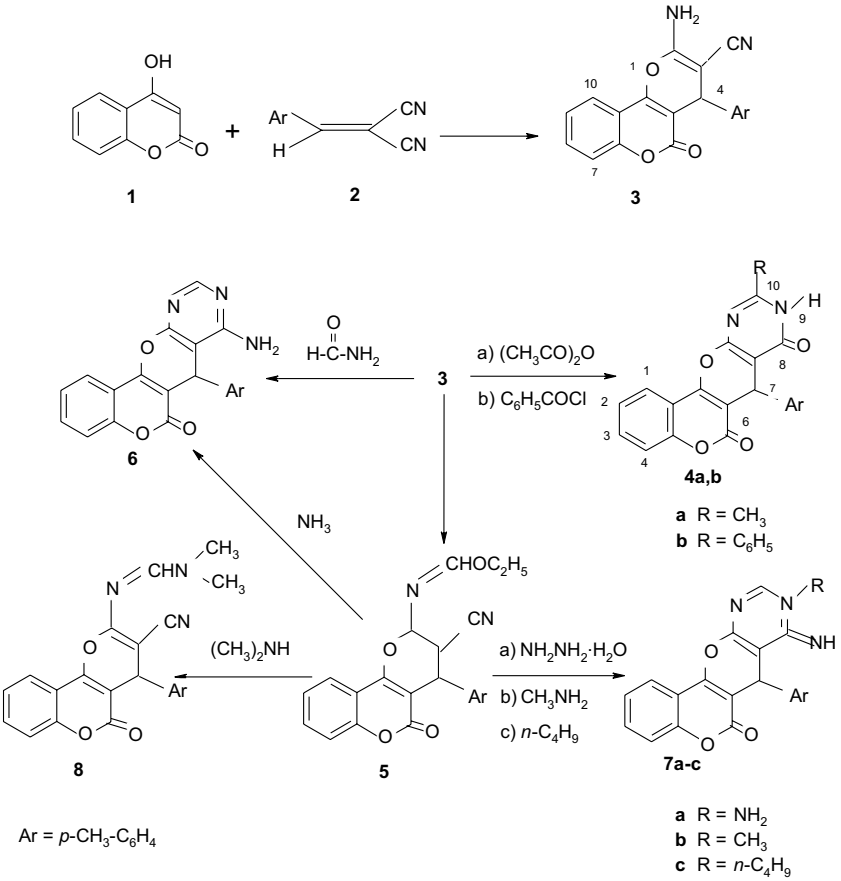
*8-Amino-7-(*p*-tolyl)-6*H,7H–[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine-6-one (**6**)*

Method A. – A solution of **3** (0.01 mol) in formamide (20 mL) was heated under reflux for 6 h to give **6** (Scheme 1) as colourless needles (benzene, m.p. 271 °C, yield 72%).

Method B. – A stream of NH_3 gas was passed through **5** (0.01 mol) in methanol for 1 h. The solid product formed was collected to give **6** (Scheme 1) (yield 84%).

*Pyranopyrimidine derivatives (**7a-c**). General procedure*

A mixture of **5** (0.01 mol) and hydrazine hydrate (5 mL, 99%), methylamine or *n*-butylamine (0.01 mol) in ethanol (50 mL) was stirred at room temperature for 1 h to give **7a-c** (Scheme 1). 9-Amino-8-imino-7-(*p*-tolyl)-6*H*,7*H*-8,9-dihydro-[1]benzopyrano[3',4':5,]-pyrano[2,3-d]pyrimidine 6-one (**7a**) (m.p. 190 °C, yield 89%), 9-methyl-8-imino-7-(*p*-tolyl)--6*H*,7*H*-8,9-dihydro-[1]benzopyrano[3',4':5,]pyrano[2,3-d]pyrimidine 6-one (**7b**), (m.p. 290 °C, yield 87%), 9-butyl-8-imino-7-(*p*-tolyl)-6*H*,7*H*-8,9-dihydro-[1]benzopyrano[3',4':5,]-pyrano [2,3-d]pyrimidine 6-one (**7c**) (m.p. 265 °C, yield 85%) were obtained as colourless crystal from dioxane.



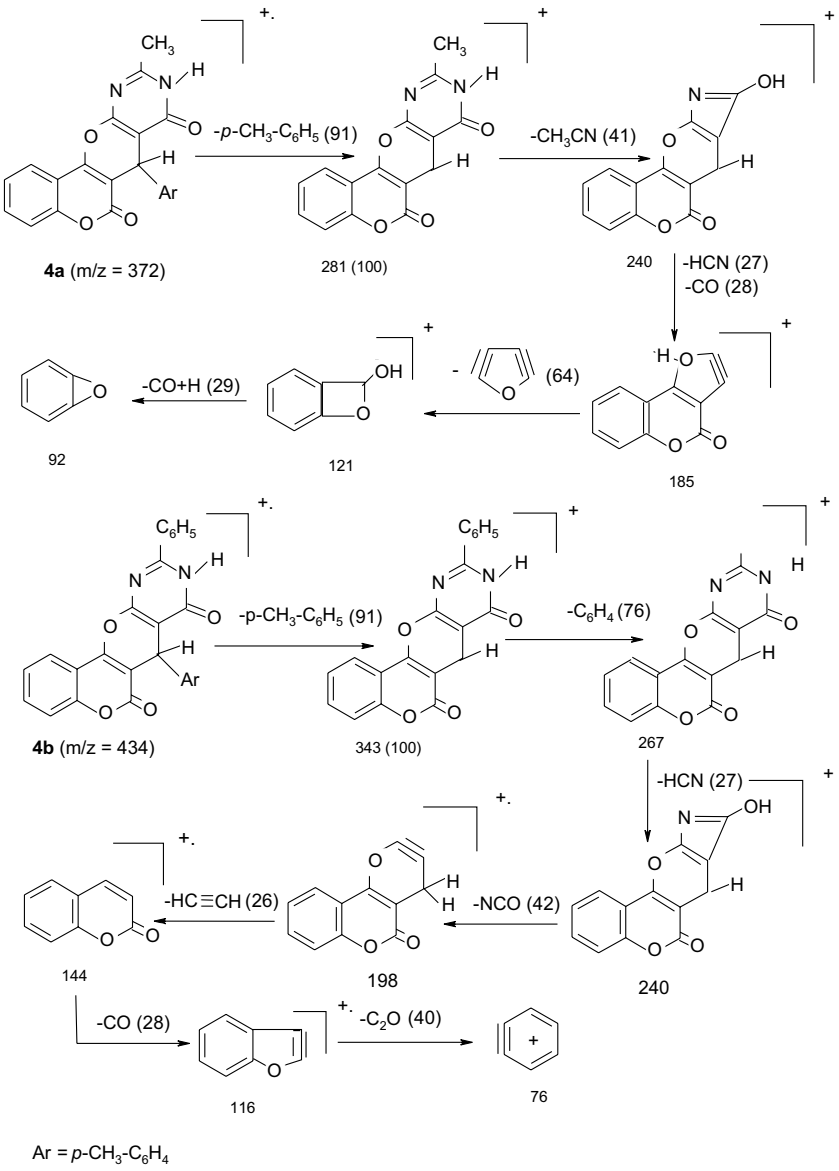
Scheme 1

*2-*N,N*-dimethylaminomethylene-5-oxo-4-(*p*-tolyl)-4*H,5*H-pyrano[3,2-c]benzopyran-3--carbonitrile (8)*

A mixture of **5** (0.01 mol) and dimethylamine (5 mL) in ethanol (50 mL) was stirred for 1 h. The white solid product was filtered, washed with cold ethanol to give **8** (Scheme 1) as colourless crystals (benzene, m.p. 278 °C, yield 83%).

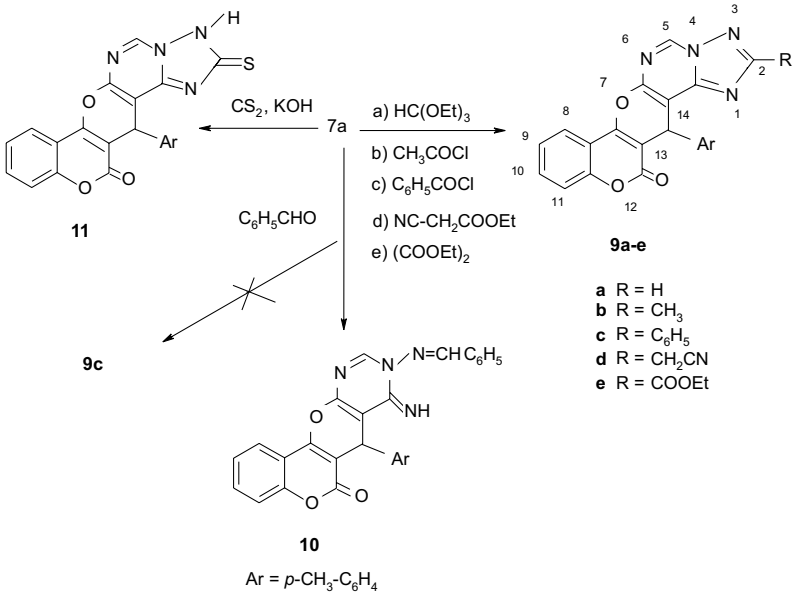
*Pyranotriazolopyrimidine derivatives (**9a-e**). General procedure*

A mixture of **7a** (3.72 g, 0.01 mol) and triethyl orthoformate or acetyl chloride or benzoyl chloride (0.01 mol) in dry benzene (20 ml) was refluxed for 3 h to give **9a-c**, while a mixture of **7a** (3.72 g, 0.01 mol) with ethyl cyanoacetate or diethyl oxalate (0.01 mol) in absolute ethanol (20 mL) gave **9d**,**e**, respectively, under the same conditions



Scheme 2

(Scheme 3). 14-(*p*-Tolyl)-13*H*,14*H*-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo-[1,5-c]--pyrimidine-13-one (**9a**) (m.p. 318 °C, yield 87%), 2-methyl-14-(*p*-tolyl)-13*H*,14*H*-[1]-benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidine-13-one (**9b**), (m.p. 314 °C,



Scheme 3

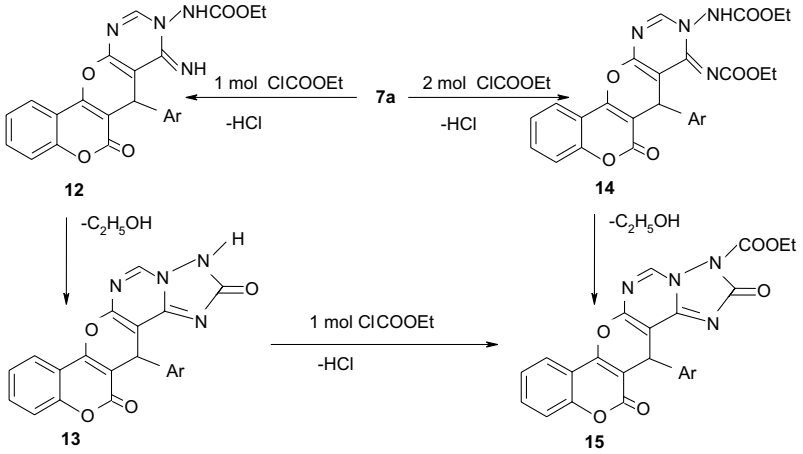
yield 87%), 2-phenyl-14-(*p*-tolyl)-13*H*,14*H*-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]-triazolo-[1,5-c]pyrimidine-13-one (**9c**) (m.p. 292 °C, yield 80%), 13-oxo-14-(*p*-tolyl)-13*H*, 14*H*-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-2-ethanenitrile (**9d**) (m.p. 310 °C, yield 85%) and ethyl-13-oxo-14-(*p*-tolyl)-13*H*,14*H*-[1]benzopyrano[3',4':5,6]-pyrano[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidine-2-carboxylate (**9e**) (m.p. 270 °C, yield 80%) were obtained as colourless crystals from dioxane.

*8-Imino-7-(*p*-tolyl)-9-phenylmethylideneamino-8,9-dihydro-6*H,7H*-[1]benzopyrano-[3',4':5,6]pyrano[2,3-d]pyrimidine-6-one (**10**)*

A mixture of **7a** (3.72 g, 0.01 mol), benzaldehyde (0.01 mol), piperidine (0.05 mL) and dioxane (30 mL) was refluxed for 6 h. The precipitate was filtered and washed several times with cold ethanol to give **10** (Scheme 3) as colourless crystals (dioxane, m.p. 300 °C, yield 84%).

*14-(*p*-tolyl)-13-oxo-*2H,13H,14H*-2,3-dihydro[1]benzopyrano[3',4':5,6]pyrano[3,2-e]-[1,2,4]triazolo[1,5-c]pyrimidine-2-thione (**11**)*

A mixture of **7a** (0.01 mol), ethanol (30 mL), KOH (0.01 mol) and carbon disulfide (3 mL) was refluxed for 5 h. After removal of the solvent, water was added and the alkaline solution was acidified with acetic acid to give **11** (Scheme 3). Compound **11** was separated as pale yellow crystals (dioxane, m.p. 280 °C, yield 76%).



Scheme 4

*4-Ethyl-14-(*p*-tolyl)-2-oxo-2H,3H,13H,14H-2,3-dihydro-[1]benzopyrano[3',4':5,6]-pyrano-[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-13-one-3-carboxylate (**15**)*

A mixture of **7a** (0.01 mol) and ethyl chloroformate (0.02 mol) in dry benzene (30 mL) was refluxed for 3 h. Colourless crystals of **15** (dioxane, m.p. 252 °C, yield 72%), were collected by filtration, to give **15** (Scheme 4). All structures of the newly synthesized compounds were established by spectral data (Table II).

Antimicrobial activity

The newly synthesized compounds were screened for their antimicrobial activity *in vitro* against six species of Gram positive bacteria, *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579), *Bacillus subtilis* (NCTC-10400) and Gram negative bacteria, namely, *Escherichia coli* (NCTC-10410), *Serratia marcescens* (IMRU-70), *Proteus mirabilis* (NTCC-289), using the paper disc diffusion method (26).

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1 mg mL^{-1}. 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 zone. Ampicillin standard was used as a reference.

RESULTS AND DISCUSSION

Condensation of 4-hydroxycoumarin with α-cyano-*p*-methyl-cinnamonitrile (**2**) afforded 2-amino-3-cyano-4-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-c][1]benzopyran-5-one (**3**) (16). Treatment of **3** with acetic anhydride afforded 10-methyl substituted benzopyrano-

Table I. Elemental analyses of new compounds

Compound No.	Molecular formula (M_r)	Analysis (%) Found/calculated		
		C	H	N
4a	$C_{22}H_{16}N_2O_4$	70.85	4.20	7.41
	(372.38)	70.95	4.33	7.52
4b	$C_{27}H_{18}N_2O_4$	74.52	4.05	6.31
	(434.45)	74.64	4.17	6.44
5	$C_{23}H_{18}N_2O_4$	71.35	4.56	7.13
	(386.40)	71.49	4.69	7.24
6	$C_{21}H_{15}N_3O_3$	70.47	4.12	11.63
	(357.37)	70.58	4.23	11.75
7a	$C_{21}H_{16}N_4O_3$	67.68	4.20	12.74
	(372.38)	67.73	4.33	12.88
7b	$C_{22}H_{17}N_3O_3$	71.02	4.50	11.19
	(371.39)	71.14	4.61	11.31
7c	$C_{25}H_{23}N_3O_3$	72.49	5.52	10.08
	(413.41)	72.62	5.60	10.16
8	$C_{23}H_{19}N_3O_3$	71.53	4.85	10.78
	(385.42)	71.67	4.96	10.90
9a	$C_{22}H_{14}N_4O_3$	69.08	3.56	14.48
	(382.38)	69.10	3.69	14.65
9b	$C_{23}H_{16}N_4O_3$	69.54	3.92	14.07
	(396.40)	69.68	4.06	14.13
9c	$C_{28}H_{18}N_4O_3$	73.24	3.81	12.14
	(458.47)	73.35	3.95	12.22
9d	$C_{24}H_{15}N_5O_3$	68.29	3.46	16.50
	(421.41)	68.40	3.58	16.61
9e	$C_{25}H_{18}N_4O_5$	65.93	3.86	12.27
	(454.44)	66.07	3.99	12.32
10	$C_{28}H_{20}N_4O_3$	72.99	4.23	12.07
	(460.49)	73.03	4.37	12.16
11	$C_{22}H_{14}N_4O_3$	63.62	3.34	13.40
	(414.44)	63.75	3.40	13.51
15	$C_{25}H_{18}N_4O_6$	63.69	3.70	11.81
	(470.44)	63.82	3.85	11.90

[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8-dione derivative **4a**, whereas the reaction of **3** with benzoylchloride gave the corresponding 10-phenyl pyrimidine derivative **4b**. Treatment of **3** with formamide afforded the aminopyrimidine derivative **6**. Interaction of **3** with triethyl orthoformate gave the corresponding ethoxymethyleneamino derivative **5**. Hydrazinolysis of **5** in ethanol at room temperature yielded 9-amino-8-imino-7-(*p*-tolyl)--6*H*,7*H*-8,9-dihydro[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine-6-one (**7a**).

Table II. Spectral data of the prepared compounds

Compound No.	IR (ν, cm^{-1})	^1H NMR (δ, ppm)/MS
4a	3388 (NH), 1711 (CO δ-lacton), 1665 (CO)	m/z 372 (M^+, 32.10%), 281 (100), 240 (124), 185 (0.52), 121 (8.1), 92 (40.70)
4b	3275 (NH), 1715 (CO δ-lacton), 1660 (CO)	m/z 434 (M^+, 5.70%), 343 (100), 267 (46.38), 198 (0.97), 144 (0.87), 116 (3.38), 100 (1.60), 76 (3.32)
5	2982, 2980 (CH stretching), 2216 (CN), 1709 (CO δ-lacton), 1666 (C=N)	1.44 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.61 (q, 2H, CH_2), 4.74 (s, 1H, pyran CH), 7.19–7.82 (m, 8H, aromatic H), 8.94 (s, 1H, CH)
6	3392, 3340 (NH_2), 1711 (CO δ-lacton)	2.92 (s, 3H, CH_3), 4.90 (s, 1H, pyran CH), 4.96 (br, 2H, NH_2), 7.10–8.12 (m, 8H, aromatic H), 8.35 (s, 1H, pyrimidine CH)
7a	3390, 3310 (NH_2), 3192 (NH), 1715 (CO δ-lacton)	2.22 (s, 3H, CH_3), 4.90 (s, 1H, pyran CH), 5.75 (br, 2H, NH_2), 7.01–7.90 (m, 10H, aromatic H + NH), 8.17 (s, 1H, pyrimidine CH)
7b	3348 (NH), 1728 (CO δ-lacton)	2.25 (s, 3H, CH_3), 3.41 (s, 3H, N–CH_3), 4.83 (s, 1H, pyran CH), 7.07–8.02 (m, 9H, aromatic H + NH), 8.17 (s, 1H, pyrimidine CH)
7c	3220 (NH), 1725 (CO δ-lacton)	
8	2202 (CN), 1720 (CO δ-lacton	2.28 (s, 3H, CH_3), 3.14 (s, 3H, N–CH_3), 3.19 (s, 3H, N–CH_3), 4.64 (s, 1H, pyran CH), 7.08–7.81 (m, 8H, aromatic H + NH), 8.22 (s, 1H, N=CH)
9a	1720 (CO δ-lacton)	2.19 (s, 3H, CH_3), 5.40 (s, 1H, pyran CH), 7.04– 8.08 (m, 8H, aromatic H), 8.63 (s, 1H, triazolo CH), 9.76 (s, 1H, pyrimidine CH)
9b	1728 (CO δ-lacton)	2.19 (s, 3H, CH_3), 3.34 (s, 3H, triazolo CH_3), 5.34 (s, 1H, pyran CH), 7.04–8.04 (m, 8H, aromatic H), 9.60 (s, 1H, pyrimidine CH)
9c	1725 (CO δ-lacton)	2.20 (s, 3H, CH_3), 5.48 (s, 1H, pyran CH), 7.08–8.20 (m, 13H, aromatic H), 8.63 (s, 1H, triazolo CH), 9.76 (s, 1H, pyrimidine CH)
9d	2198 (CN), 1712 (CO δ-lacton)	2.19 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 5.33 (s, 1H, pyran CH), 7.05–7.99 (m, 8H, aromatic H), 9.75 (s, 1H, pyrimidine CH)
9e	1741 (CO ester), 1720 (CO δ-lacton)	1.48 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 4.54 (q, 2H, CH_2), 5.81 (s, 1H, pyran CH), 7.08–8.15 (m, 8H, aromatic H), 9.26 (s, 1H, pyrimidine CH)
10	3295 (NH), 1700 (CO δ-lacton)	2.16 (s, 3H, CH_3), 6.02 (s, 1H, pyran CH), 7.01–8.01 (m, 13H, aromatic H), 8.23 (s, 1H, N=CH), 8.46 (s, 1H, pyrimidine CH), 11.19 (br, 1H, C=NH)
11	3487 (NH), 1720 (CO δ-lacton), 1042 (C=S)	2.27 (s, 3H, CH_3), 5.10 (s, 1H, pyran CH), 7.05 (br, 1H, NH), 7.29–8.01 (m, 8H, aromatic H), 8.18 (s, 1H, pyrimidine CH)
15	1750 (CO ester), 1733 (CO δ-lacton), 1716 (CO)	1.32 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 4.43 (q, 2H, CH_2), 5.07 (s, 1H, pyran CH), 7.07–8.04 (m, 8H, aromatic H), 9.39 (s, 1H, pyrimidine CH)

Aminolysis of **5** with aliphatic primary amines gave the corresponding pyranopyrimidine-6-one derivatives **7b**,**c**, and with dimethylamine the dimethylaminomethyleneamino derivative **8**. Amminolysis of **5** gave 8-amino-7-(*p*-tolyl)-6*H*,7*H*[1]benzopyrano[3',4':5,6]pyrano[2,3-d]pyrimidine-6-one (**6**).

Structures **4a,b** were established on the basis of spectral data: the mass spectrum of **4a,b** showed molecular ion peaks m/z 372 (M^+, 32.01%) and m/z 434 (M^+, 5.70%), respectively. The fragmentation pattern of compounds **4a,b** is illustrated in Scheme 2.

Structures **5**–**8** were established by spectral data (Table II). Treatment of **7a** with some carboxylic acid chlorides gave the corresponding 14-(*p*-tolyl)-2-substituted-13*H*,14*H*-[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-13-one (**9b**,**c**), while cyclocondensation of **7a** with ethyl cyanoacetate or diethyl oxalate gave the corresponding 2-cyanomethyl and 2-ethoxycarbonyl derivatives **9d**,**e**, respectively. Also, **7a** reacted with triethyl orthoformate to afford the corresponding [1,2,4]triazolo[1,5-c] pyrimidine-13-one derivative **9a**, while **7a,** when reacted with benzaldehyde, gave the pyrimidine derivative **10** instead of the expected triazolopyrimidine derivative **9c**. The reaction of **7a** with alcoholic CS_2-KOH gave 14-(*p*-tolyl)-13-oxo-2*H*,13*H*,14*H*-2,3-dihydro[1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-2-thione (**11**).

Treatment of **7a** with ethyl chloroformate in dry benzene afforded 1:2 adducts **15** (Scheme 4). Formation of **15** is assumed to proceed *via* interaction of **7a** with one mole ethyl chloroformate with elimination of HCl to yield **12**. Compound **12** then cyclized

Table III Antibacterial activity of new compounds

Compd. No.	Inhibition zone diameter (mm)					
	Staphylococcus aureus (NCTC-7447)	*Bacillus cereus* (ATCC-14579)	*Bacillus subtilis* (NCTC-10400)	*Serratia marcesces* (IMRU-70)	*Proteus mirabilis* (NTCC-289)	*Escherichia coli* (NCTC-10410)
4a	13	16	16	10	15	14
4b	10	12	15	14	18	15
5	11	10	–	11	13	–
6	14	15	17	10	16	13
7a	12	18	15	14	12	14
7b	13	17	14	12	17	12
7c	10	12	16	14	18	16
8	15	14	–	15	16	–
9a	23	22	20	20	23	20
9b	22	23	20	21	20	20
9c	23	24	20	24	22	23
9d	24	23	15	23	20	21
9e	22	23	22	25	23	20
10	9	15	–	13	14	–
11	25	23	19	24	23	11
15	24	21	17	20	22	14
Ampicillin (25 μg mL^{-1})	22	22	20	22	22	18

into **13** with elimination of ethanol and then reacted with another mole ethyl chloroformate with elimination of HCl to give **15**. The other way of synthesizing compound **15** is the reaction of **7a** with two moles of ethyl chloroformate in one step to yield bis(ethoxycarbonyl) derivative **14**, which cyclized into **15** with elimination of ethanol.

CONCLUSIONS

Strong antibacterial activity against five strains of bacteria exceeding that of ampicilin as a reference, was found for novel [1]benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives synthesized in this work. It may be concluded that compounds containing both pyrimidine and triazole moieties show improved antibacterial activity compared to ampicillin. Contrary to this, compounds containing pyran or pyrimidine moiety show antibacterial activity lower than that of ampicillin.

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S A Ž E T A K

Aktivirani nitrili u sintezi heterocikala: Sinteza novih [1]benzopirano[3',4':5,6]pirano[2,3-d]pirimidin i [1]benzopirano[3',4':5,6]pirano[3,2-e][1,2,4]triazolo[1,5-c]-pirimidin derivata s potencijalnim antibakterijskim djelovanjem

ASHRAF H. F. ABD EL-WAHAB

2-Amino-5-okso-pirano[3,2-c]benzopiran-3-karbonitril derivati (**3**) upotrebljeni su kao prekursori za sintezu novih benzopirano[3',4':5,6]pirano[2,3-d]pirimidina (**4, 6, 7** i **10**), benzopirano[3',4':5,6]pirano[3,2-e][1,2,4]triazolo[1,5-c]pirimidina (**9, 11** i **15**) i 2-amino derivata pirano[3,2-c][1]benzopirana (**5, 8**). Novi spojevi testirani su na antibakterijsko djelovanje.

Ključne riječi: pirano[3,2-c]benzopirani, pirano[2,3-d]pirimidini, [1,2,4]triazolo[1,5-c]pirimidini, antibakterijsko djelovanje

Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City 11884 Cairo, Egypt