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Synthesis and antimicrobial evaluation of naphtho[2,1-b]pyrano[2,3-d]pyrimidine and pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives

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Several novel naphtho[2,1-b]pyrano[2,3-d]pyrimidines, pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines and their coumarin-3-yl derivatives were synthesized. Some of these derivatives exhibited pronounced antimicrobial activities.

Keywords: pyranopyrimidine derivatives, pyranotriazolopyrimidine derivatives, coumarin-3-yl-pyranotriazolopyrimidine derivatives, antibacterial activity

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Pyrane and fused 4*H*-pyrane derivatives have attracted a great deal of interest owing to their antimicrobial activity (1-3), inhibition of influenza, virus sialidases (4), mutagenic activity (5), activity as antiviral (6) and antiproliferaction agents (7), sex-pheromones (8) antitumor (9) and anti-inflammatory agents (10). Moreover, pyrane derivatives are well known for their antihistaminic activity (11). Also, pyrimidines and fused pyrimidines play an essential role in several biological processes and have a considerable chemical and pharmacological importance. In particular, pyrimidine nucleus can be found in a broad variety of antibacterial and antitumor agents as well as in agrochemical and veterinary products (12-15).

In continuation of the previous works (16, 17), it seemed interesting to synthesize new methoxy-4*H*-naphtho[1',2':5,6]-pyrano[2,3-d]pyrimidine, pyrano[3,2-e][1,2,4[triazolo [2,3-c]pyrimidine and their coumarin-3-yl derivatives by using 2-amino-7-methoxy-4--(*p*-tolyl)-4*H*-naphtho[2,1-b]pyrane-3-carbonitrile as starting material. These derivatives might be active against some Gram-positive and Gram-negative organisms.

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EXPERIMENTAL

Melting points were measured using the 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 and ^{13}C NMR spectra were measured on a Varian Mercury (300 MHz) spectrometer (Varian, UK), using tetramethylsilane (TMS) as the internal standard and (DMSO-d_6) as solvent. Microanalytical data (Table I) were obtained from the Microanalytical Unit of the Cairo University (Egypt).

*Synthesis of 4*H*-pyrane derivatives (**3a-f**). General procedure*

A mixture of substituted α-cyano-cinnamonitriles (**2a-c**) (0.01 mol) and/or ethyl-2--cyano-3-aryl acrylate (**2d-f**) (0.01 mol), 6-methoxy-2-naphthol (**1**) (0.01 mol) and piperidine (0.5 mL) in absolute ethanol (50 mL) was heated until precipitation was completed. The precipitate was collected by filtration and recrystallized from the suitable solvent.

2-Amino-4-aryl-7-methoxy-4*H*-naphtho[2,1-b]pyrane-3-carbonnitrile (**3a-c**) and ethyl 2-amino-4-aryl-7-methoxy-4*H*-naphtho[2,1-b]pyrane-3-carboxylate (**3d-f**) afforded colourless needles from dioxane and ethanol, respectively.

*Synthesis of 2-acetylamino-7-methoxy-4-(*p*-tolyl)-4*H*-naphtho[2,1-b]pyrane--3-carbonitrile (**4a**)*

A solution of **3a** (0.01 mol) in Ac_2O (20 mL) was heated under reflux for 30 min. The solid product formed was filtered off and washed with cold EtOH to give **4a** as pale yellow crystals (from ethanol).

*Synthesis of 2-benzoylamino-7-methoxy-4-(*p*-tolyl)-4*H*-naphtho[2,1-b]-pyrane-3-carbonitrile (**4b**)*

A solution of **3a** (0.01 mol) in benzoyl chloride (20 mL) was heated under reflux for 30 min. The excess of benzoyl chloride was removed under reduced pressure and the residue was poured into water. The precipitate was collected by filtration, washed with carbon tetrachloride (10 mL) to remove the formed benzoic acid and the residue was dried to give **4b** as colourless crystals from DMF.

*Synthesis of 10,11-dihydro-3-methoxy-9-methyl-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]pyrimidine-11-one (**5a**)*

Method A. – A solution of **3a** (0.01 mol) in Ac_2O (20 mL) was heated under reflux for 6 h. The precipitate was filtered off, washed with cold EtOH to give **5a** as colourless crystals from DMF.

Method B. – Gaseous dry HCl was bubbled through the mixture of **3b** (0.01 mol) and CH_3CN (30 mL) for 4-6 h. The reaction mixture was poured into ice water and alkalized with 10% aqueous ammonium hydroxide to give **5a**.

*Synthesis of 10,11-dihydro-3-methoxy-9-phenyl-12-(*p*-tolyl)-12*H*-naphtho[2,1-b]-pyrano[2,3-d]pyrimidine-11-one (**5b**)*

A solution of **3a** (0.01 mol) in benzoyl chloride (20 mL) was heated under reflux for 6 h. The excess of benzoyl chloride was removed under reduced pressure and the residue was poured into cold water. The precipitate was collected by filtration, washed with carbon tetrachloride (10 mL) to remove the formed benzoic acid and the residue was dried to give **5b** as colourless crystals from DMF.

*Synthesis of 2-ethoxymethyleneamino-7-methoxy-4-(*p*-tolyl)-4*H*-naphtho-[2,1-b]pyrane-3-carbonitrile (**6**)*

A mixture of **3a** (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 off and washed several times with cold ethanol to give **6** as colourless crystals from benzene.

*Synthesis of pyranopyrimidine derivatives (**7a,b**). General procedure*

A mixture of **6** (0.01 mol), hydrazine hydrate (5 mL, 99%) or methylamine (0.01 mol) in absolute ethanol (50 mL) was stirred for 1 h at room temperature to give **7a,b**. 10-Amino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho[2,1-b]pyrano[2,3-d]pyrimidine (**7a**) and 10,11-dihydro-11-imino-3-methoxy-10-methyl-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]pyrimidine (**7b**) were obtained as colourless crystals from dioxane.

*Synthesis of 7-methoxy-2-(*N,N*-dimethylaminomethylene)-4-(*p*-tolyl)-4*H*-naphtho[2,1-b]pyrane-3-carbonitrile (**8**)*

A mixture of **6** (0.01 mol) and dimethylamine (5 mL) in ethanol was stirred for 1 h. The white solid formed was filtered, washed with cold ethanol to give **8** as colourless crystals from benzene.

*Synthesis of 10,11-dihydro-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]-pyrimidine-11-thione (**9**)*

H_2S was bubbled through a solution of **6** (0.01 mol) in absolute ethanol (50 mL) at room temperature for 1 h. The reaction mixture was stirred for an additional hour to give **9** as yellow crystals from dioxane.

*Synthesis of 11-amino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]pyrimidine (**10**)*

Method A. – Gaseous NH_3 was bubbled through **6** (0.01 mol) in methanol for 1 h. The solid formed was collected to give **10** as colourless needles from benzene.

Method B. – A solution of **3a** (0.01 mol) in formamide (20 mL) was heated under reflux for 6 h to give **10.**

*Synthesis of pyranotriazolopyrimidine derivatives (**11a-e**). General procedure*

A mixture of **7a** (3.72 g, 0.01 mol), triethyl orthoformate, acetyl chloride or benzoyl chloride (0.01 mol) in dry benzene (20 mL) was refluxed for 3 h to give **11a-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) under the same conditions gave **11d,e**, respectively (Scheme 2). 11-Methoxy-14-(*p*-tolyl)-14*H*-naphtho[2,1-b]pyrano[3,2-e][1,2,4]triazo-lo[1,5-c]pyrimidine (**11a**), 2-methyl-11-methoxy-14-(*p*-tolyl)-14*H*-napht-ho[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine (**11b**), 2-phenyl-11-methoxy-14-(*p*-tolyl)-14*H*-naphtho[2,1-b]pyrano[3,2-e][1,2,4] triazolo[1,5-c]pyrimidine (**11c**), 11-methoxy-14-(*p*-tolyl)-14*H*-naphtho[2,1-b]pyrano[3,2-e] [1,2,4]triazolo[1,5-c]pyrimidine-2-ethanenitrile (**11d**) and ethyl 11-methoxy-14-(*p*-tolyl)-14*H*--naphtho[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-2-carboxylate (**11e**) were obtained as colourless crystals from dioxane.

*Synthesis of 10-benzalamino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho[2,1-b]pyrano[2,3-d]pyrimidine (**12**)*

A mixture of **7a** (3.72 g, 0.01 mol), benzaldehyde (0.01 mol), piperidine (0.5 mL) and dioxane (30 mL) was refluxed for 6 h. The precipitate was filtered off and washed several times with cold ethanol to give **12** as colourless crystals from dioxane.

*Synthesis of ethyl 14-(p-tolyl)-11-methoxy-2-oxo-2H,3H,14H-naphtho[2,1-b]-pyrano[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine-3-carboxylate (**13**)*

A mixture of **7a** (0.01 mol) and ethyl chloroformate (0.02 mol) in dry benzene (30 mL) was refluxed for 3 h to give **13** as colourless crystals from dioxane.

*Synthesis of 2-(coumarin-3-yl)-11-methoxy-14-(*p*-tolyl)-14*H*-naphtho[2,1-b]-pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**14a**)*

A mixture of **11d** (0.01 mol), salicylaldehyde (0.01 mol) and dioxane (30 mL) was refluxed for 3 h. The precipitate was filtered off and washed several times with cold ethanol to give **14a** as colourless crystals from dioxane.

*Synthesis of 2-(benzo-5:6-coumarin-3-yl)-11-methoxy-14-(*p*-tolyl)-14*H*-naphtho-[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**14b**)*

A mixture of **11d** (0.01 mol), 2-hydroxynaphthaldehyde (0.01 mol) and dioxane (30 mL) was refluxed for 3 h. The precipitate was filtered off and washed several times with cold ethanol to give **14b** as colourless crystals from dioxane.

Structures **3-14** were established by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral data (Tables I and II).

Table I. Elemental analyses of the new compounds

Compd. No.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Found/calcd. (%)		
				C	H	N
3a	89	232–4	$C_{22}H_{18}N_2O_2$	77.09	5.18	8.02
			(342.38)	77.17	5.29	8.18
3b	87	220–2	$C_{21}H_{16}N_2O_3$	73.25	4.65	8.10
			(344.00)	73.30	4.70	8.15
3c	86	246–7	$C_{22}H_{18}N_2O_3$	73.60	5.06	7.65
			(358.39)	73.73	4.89	7.81
3d	74	185–8	$C_{24}H_{23}NO_4$	73.82	5.65	3.23
			(389.44)	74.02	5.96	3.59
3e	70	177–9	$C_{24}H_{23}NO_5$	69.07	5.60	3.31
			(405.45)	69.17	5.71	3.45
3f	72	170–2	$C_{23}H_{21}NO_4$	73.40	5.46	3.51
			(375.41)	73.58	5.63	3.73
4a	80	216–8	$C_{24}H_{20}N_2O_3$	74.90	5.22	7.25
			(384.90)	74.98	5.24	7.29
4b	83	295–8	$C_{29}H_{22}N_2O_3$	77.85	4.79	6.24
			(446.50)	78.01	4.96	6.27
5a	75	> 360	$C_{24}H_{20}N_2O_3$	74.62	5.03	5.46
			(384.43)	74.98	5.24	5.83
5b	70	> 360	$C_{29}H_{22}N_2O_3$	77.90	4.77	6.23
			(446.50)	78.01	4.96	6.27
6	75	185–8	$C_{25}H_{22}N_2O_3$	75.12	5.38	6.98
			(398.45)	75.35	5.56	7.03
7a	88	230–2	$C_{23}H_{20}N_4O_2$	71.65	5.10	14.47
			(384.43)	71.85	5.24	14.57
7b	85	265–7	$C_{24}H_{21}N_3O_2$	75.04	5.31	10.82
			(383.45)	75.17	5.52	10.95
8	85	272–5	$C_{25}H_{23}N_3O_2$	75.52	5.80	10.50
			(397.50)	75.54	5.83	10.57
9	70	268–70	$C_{23}H_{18}N_2O_2S$	71.25	4.35	7.09
			(386.47)	71.48	4.66	7.24
10	82	292–5	$C_{24}H_{15}N_3O_3$	73.20	3.81	10.68
			(393.41)	73.25	3.85	10.72
11a	88	272–4	$C_{24}H_{18}N_4O_2$	72.99	4.48	14.13
			(394.42)	73.08	4.59	14.20
11b	85	284–6	$C_{25}H_{20}N_4O_2$	73.29	4.75	13.84
			(408.46)	73.51	4.93	13.71
11c	81	276–8	$C_{30}H_{22}N_4O_2$	76.37	4.52	11.75
			(470.53)	76.57	4.71	11.90
11d	80	285–8	$C_{26}H_{19}N_5O_2$	72.00	4.34	16.01
			(433.46)	72.04	4.41	16.15

Table I. continued

11e	83	285–7	$C_{27}H_{22}N_4O_4$	69.15	4.50	11.97
			(466.50)	69.32	4.57	12.01
12	84	238–40	$C_{30}H_{24}N_4O_2$	76.18	5.03	11.74
			(472.54)	76.25	5.11	11.85
13	72	315–8	$C_{27}H_{22}N_4O_5$	67.10	4.21	11.30
			(482.49)	67.15	4.16	11.41
14a	84	300–2	$C_{33}H_{22}N_4O_4$	73.41	4.01	11.65
			(538.565)	73.52	4.08	11.88
14b	86	353–5	$C_{37}H_{24}N_4O_4$	75.30	4.05	9.45
			(588.64)	75.40	4.11	9.52

Table II. Spectral data of the prepared compounds

Compd. No.	IR (ν, cm^{-1})	^1H NMR/^{13}C NMR (δ, ppm) (DMSO-d_6)
3a	3433, 3332 (NH_2), 3014, 2964, 2924, 2849 (stretching CH), 2211 (CN), 1690 (C=C)	2.18 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.20 (s, 1H, pyrane CH), 6.93 (br, 2H, NH_2, exchangeable), 7.04-7.83 (m, 9H, Ar-H) 20.9 (CH_3), 27.7 (C-4), 56.0 (OCH_3), 59.2 (C-3), 105.8 (C-7), 117.2 (CN), 118.7 (C-5), 118.9 (C-9), 123.7 (C-10), 126.8 (C-6), 128.3 (Ar), 129.7 (Ar), 131.1 (C-6a), 136.5 (Ar), 143.7 (Ar), 146.2 (C-4), 157.2 (C-8), 160.5 (C-3)
3b	3403, 3322 (NH_2), 3058, 2965, 2926 (stretching CH) 2195 (CN), 1660 (C=C)	3.33 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.20 (s, 1H, pyrane CH), 6.82 (br, 2H, NH_2 exchangeable), 6.82-7.82 (m, 9H, Ar-H)
3c	3446, 3335 (NH_2), 3017, 2924, 2849 (stretching CH), 2211 (CN), 1690 (C=C)	3.80 (s, 3H, OCH_3), 5.25 (s, 1H, pyrane CH), 6.94 (br, 2H, NH_2, exchangeable), 7.16-7.81 (m, 10H, Ar-H)
3d	3434, 3304 (NH_2), 2992, 2920, 2832 (stretching CH), 1675 (CO)	1.39 (t, 3H, CH_3, J = 7.1Hz), 2.16 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.23 (q, 2H, CH_2, J = 7.1Hz), 5.30 (s, 1H, pyrane CH), 6.30 (br, 2H, NH_2, exchangeable), 6.99-7.88 (m, 9H, Ar-H)
3e	3425, 3312 (NH_2), 2921, 2865 (stretching CH), 1672 (CO)	1.36 (t, 3H, CH_3, J = 7.1Hz), 3.72 (s, 3H, OCH3), 3.81 (s, 3H, OCH_3), 4.25 (q, 2H, CH_2, J = 7.1Hz), 5.53 (s, 1H, pyrane CH), 6.31 (br, 2H, NH_2, exchangeable), 7.01-7.91 (m, 9H, Ar-H)
3f	3410, 3311 (NH_2), 2990, 2930, 2872 (stretching CH), 1665 (CO)	1.36 (t, 3H, CH_3, J = 7.1Hz), 3.80 (s, 3H, OCH_3), 4.25 (q, 2H, CH_2, J = 7.1Hz), 5.53 (s, 1H, pyrane CH), 6.30 (br, 2H, NH_2, exchangeable), 6.99-7.88 (m, 10H, Ar-H)
4a	3444 (NH), 3026, 3007, 2957, 2923 (stretching CH), 2216 (CN), 1733 (CO)	2.16 (s, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 5.78 (s, 1H, pyrane CH), 7.10-7.91 (m, 9H, Ar-H), 10.59 (br, 1H, NH, exchangeable)
4b	3353 (NH), 3041, 2957, 2923 (stretching CH), 2218 (CN), 1728 (CO)	2.16 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.78 (s, 1H, pyrane CH), 7.12-7.97 (m, 14H, Ar-H), 11.10 (br, 1H, NH, exchangeable)
5a	3432 (NH), 3001, 2981, 2920 (stretching CH), 1660 (CO)	2.30 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.79 (s, 3H, O CH_3), 5.74 (s, 1H, pyrane CH), 7.30-8.60 (m, 10H, Ar-H + NH)

Table II. continued

5b	3320 (NH), 3001, 2960 (stretching CH) 1665 (CO)	2.28 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.76 (s, 1H, pyrane CH), 7.35-8.12 (m, 15H, Ar-H + NH)
6	3040, 2985, 2951 (stretching CH), 2205 (CN), 1650 (C=N)	1.41 (t, 3H, CH_3, J = 7.1Hz), 2.28 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.45 (q, 2H, CH_2, J = 7.1Hz), 5.28 (s, 1H, pyrane CH), 7.09-7.18 (m, 9H, Ar-H), 8.42 (s, 1H, N=CH)
7a	3314, 3265 (NH_2), 3200 (NH), 2948, 2899 (stretching CH), 1646 (C=N)	2.13 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 5.68 (s, 1H, pyrane CH), 5.81 (br, 2H, NH_2, exchangeable), 6.90-7.81 (m, 10H, Ar-H +NH), 8.16 (s, 1H, pyrimidine)
7b	3375 (NH), 3002, 2981, 2829 (stretching CH), 1620 (C=N)	2.13 (s, 3H, CH_3), 3.35 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 6.02 (s, 1H, pyrane CH), 7.01-7.92 (m, 9H, Ar-H), 8.27 (s, 1H, pyrimidine CH)
8	2984, 2925 (stretching CH), 2205 (CN), 1621 (C=N)	2.12 (s, 3H, CH_3), 3.11 (s, 3H, NCH_3), 3.4 (s, 3H, NCH_3), 5.64 (s, 1H, pyrane CH), 7.01-7.98 (m, 9H, Ar-H), 8.52 (s, 1H, N=CH)
9	3325 (NH), 2948, 2899 (stretching CH), 1646 (C=N), 1043 (C=S)	2.13 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.08 (s, 1H, pyrane CH), 6.9-7.88 (m, 10H, Ar-H+NH), 8.31 (s, 1H, pyrimidine CH)
10	3477, 3371 (NH_2), 3001, 2993, 2925 (stretching CH), 1614 (C=N), 1582 (C=C)	2.18 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.86 (br, 2H, NH_2, exchangeable), 5.68 (s, 1H, pyrane CH), 6.88-7.91 (m, 9H, Ar-H), 8.30 (s, 1H, pyrimidine CH)
11a	2984, 2925 (stretching CH), 1632 (C=C)	2.11 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.24 (s, 1H, pyrane CH), 6.98-7.91 (m, 9H, Ar-H), 8.63 (s, 1H, pyrimidine CH), 9.64 (s, 1H, 2-H)
11b	3076, 2952, 2928 (stretching CH), 1633 (C=C)	2.12 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.21 (s, 1H, pyrane CH), 6.99-7.99 (m, 9H, Ar-H), 9.51 (s, 1H, pyrimidine CH)
11c	3064, 2961, 2929 (stretching CH), 1633 (C=C)	2.14 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.41 (s, 1H, pyrane CH), 7.03-7.91 (m, 14H, Ar-H), 8.70 (s, 1H, pyrimidine CH)
11d	2995, 2936 (stretching CH), 2255 (CN), 1633 (C=C)	2.12 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 6.23 (s, 1H, pyrane CH), 6.99-7.94 (m, 9H, Ar-H), 9.64 (s, 1H, pyrimidine CH)
11e	3076, 2952 (stretching CH), 1633 (C=C)	1.38 (t, 3H, CH_3, J = 7.1Hz), 2.16 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.44 (q, 2H, CH2, J = 7.1Hz), 6.24 (s, 1H, pyrane CH), 6.99-7.92 (m, 9H, Ar-H), 9.73 (s, 1H, pyrimidine CH)
12	3261 (NH), 3067, 2981, 2924 (stretching CH), 1652 (C=N)	2.15 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.31 (s, 1H, pyrane CH), 7.01-8.01 (m, 14H, Ar-H+NH), 8.27 (s, 1H, N=CH), 9.64 (s, 1H, pyrimidine CH)
13	3025, 2987, 2924 (stretching CH) 1716 (CO)	1.39 (t, 3H, CH_3, J = 7.1Hz), 2.28 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.43 (q, 2H, CH_2, J = 7.1Hz), 6.28 (s, 1H, pyrane CH), 6.80-7.81 (m, 9H, Ar-H), 8.5 (s, 1H, pyrimidine CH)
14a	3074, 2931 (stretching CH), 1744 (CO) and 1622 (C=C)	2.12 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.28 (s, 1H, pyrane CH), 7.01-7.95 (m, 14H, Ar-H+NH), 9.05 (s, 1H, 4-H), 9.69 (s, 1H, pyrimidine CH)
14b	3026, 2931 (stretching CH), 1748 (CO) and 1635 (C=C)	2.16 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.32 (s, 1H, pyrane CH), 6.99-7.80 (m, 18H, Ar-H+NH), 9.73 (s, 1H, 4-H), 9.73 (s, 1H, pyrimidine CH)

Table III. Antimicrobial activity of the new compounds

Compd. No.[a]	Inhibition zone diameter in mm					
	Staphylococcus aureus (NCTC-7447)	*Bacillus cereus* (ATCC-14579)	*Bacillus subtilis* (NCTC-10400)	*Serratia marcescens* (IMRU-70)	*Proteus mirabilis* (NTCC-289)	*Escherichia coli* (NCTC-10410)
3a	14	12	13	12	10	14
3b	16	14	15	14	13	15
3c	13	11	12	10	11	12
3d	12	10	10	11	13	11
3e	14	13	11	14	12	10
3f	10	11	10	12	11	12
4a	10	12	–	11	–	10
4b	12	10	–	14	13	15
5a	21	20	22	23	21	19
5b	23	22	20	21	23	20
6	10	12	–	12	–	11
7a	17	18	19	23	20	21
7b	14	15	16	25	23	20
8	11	10	–	10	12	13
9	18	17	20	13	14	25
10	17	19	19	24	23	20
11a	22	21	20	23	24	20
11b	24	25	22	21	22	22
11c	22	23	24	25	26	20
11d	23	20	26	24	24	22
11e	21	22	25	26	20	20
12	20	18	21	20	21	17
13	22	20	23	22	24	18
14a	26	25	24	23	25	22
14b	27	28	26	24	28	24
Ampicillin (25 μg mL^{-1})	22	22	20	22	22	18

[a] $c = 1$ mg mL^{-1} of new compounds in DMF.

Antimicrobial activity

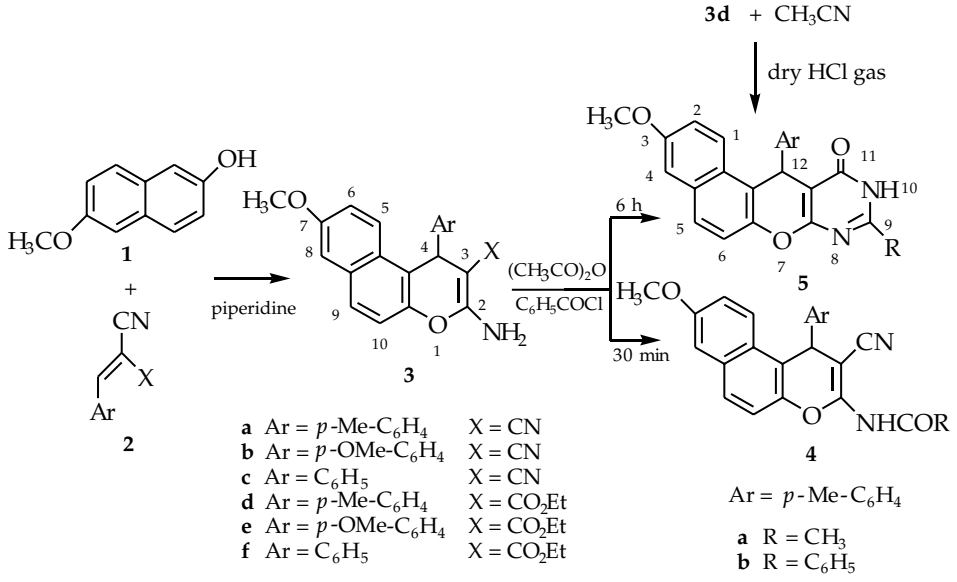
The new synthesized compounds were screened for their antimicrobial activity *in vitro* against three species of Gram-positive bacteria, *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579) and *Bacillus subtilis* (NCTC-10400) and three Gram-negative bacteria, *Escherichia coli* (NCTC-10410), *Serratia marcescens* (IMRU-70) and *Proteus mira-*

bilis (NTCC-289), using the paper disc diffusion method (18). Filter paper discs manufactured by Bristol-Myers Squibb (Egypt) were used.

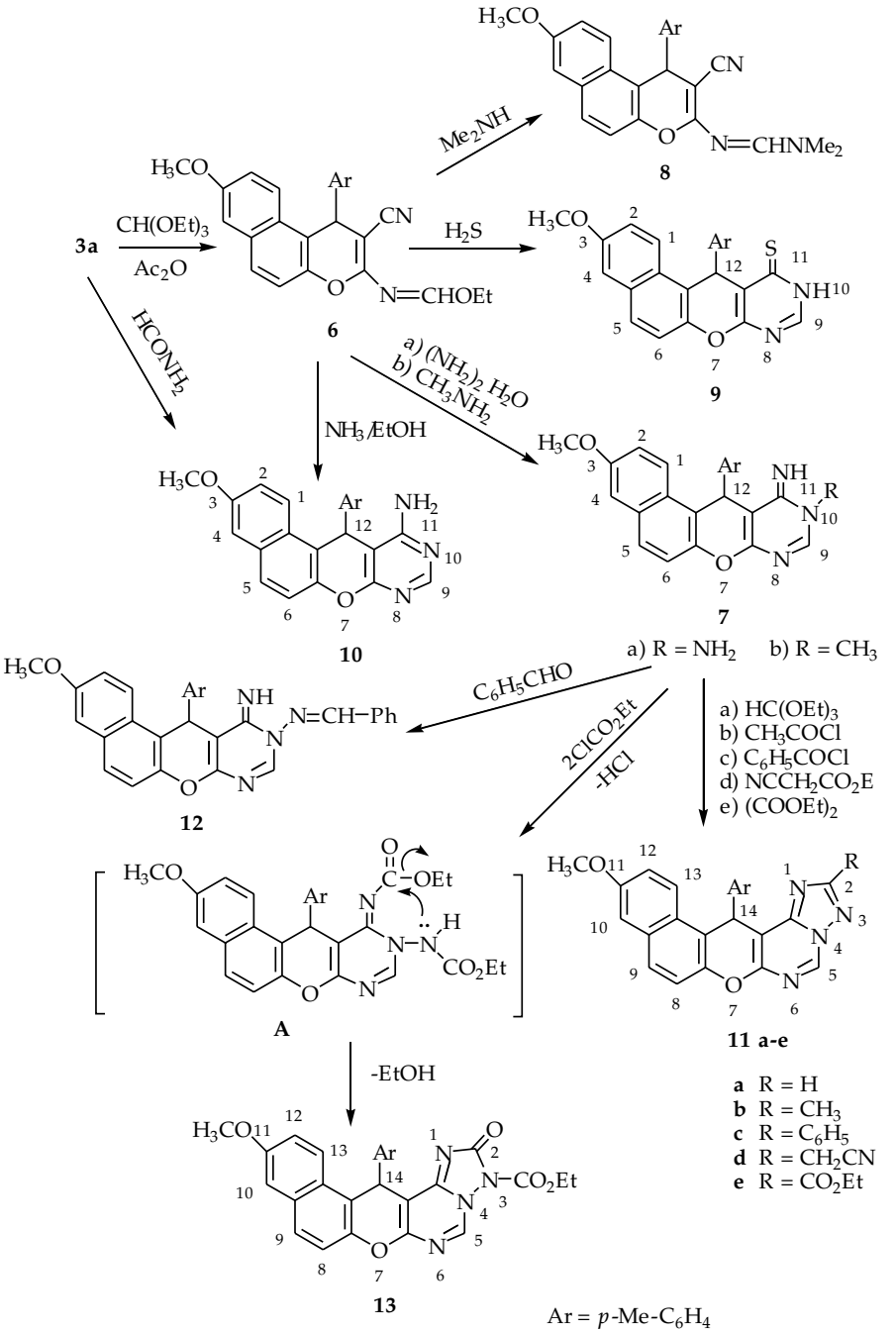
The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1 mg mL^{-1}. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zones. The ampicillin standard was used as a reference.

RESULTS AND DISCUSSION

Condensation of 6-methoxy-2-naphthol (**1**) with substituted α-cyano-cinnamonitriles (**2a**-**c**) and/or ethyl-2-cyano-3-aryl acrylate (**2d**-**f**) afforded the corresponding 2-amino--4-aryl-7-methoxy-4*H*-naphtho[2,1-b]pyrane-3-carbonitrile (**3a**-**c**) and ethyl-3-carboxylate (**3d**-**f**), respectively (19, 20). Treatment of **3a** with Ac_2O gave two products dependening on the reaction time; one product was identified as 2-acetylamino-7-methoxy-4-(*p*-tolyl)-4*H*-naphtho[2,1-b]pyrane-3-carbonitrile (**4a**) (30 min), while the other was identified as 10,11-dihydro-3-methoxy-9-methyl-12-(*p*-tolyl)-12*H*-naphtho[2,1-b]pyrano[2,3-d]pyrimidine-11-one (**5a,** 6 h). Similarly, the reaction of **3a** with benzoyl chloride gave the corresponding 2-benzoylamino-4*H*-naphthopyran-3-carbonitrile (**4b**) and 9-phenyl pyrimidine derivative (**5b**). Structure **4a** was established on the basis of IR, which showed the presence of CN at 2216 cm^{-1} and CO of the acetyl group at 1732 cm^{-1} and for **5a** the absence of CN and the presence of amide carbonyl at 1660 cm^{-1}. ^1H NMR showed a signal for $COCH_3$ and for **5a** a signal for 9-CH_3. Unequivocal support for structure **5** was ob-



Scheme 1

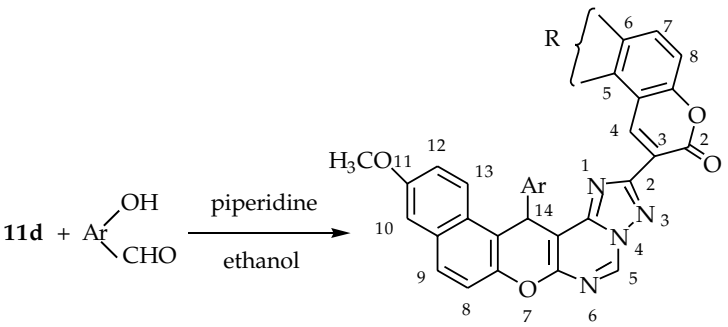

3a
CH(OEt)3
Ac2O
Me2NH
H2S
HCONH2
NH3/EtOH
a) (NH2)2 H2O
b) CH3NH2
C6H5CHO
2ClCO2Et
-HCl
-EtOH
a) HC(OEt)3
b) CH3COCl
c) C6H5COCl
d) NCCH2CO2E
e) (COOEt)2
6
8
9
10
7
12
A
11 a-e
13
a) R = NH2 b) R = CH3
a R = H
b R = CH3
c R = C6H5
d R = CH2CN
e R = CO2Et
Ar = p-Me-C6H4

Scheme 2

tained by the independent synthesis of **5a** by the reaction of **3d** with CH_3CN in the presence of dry HCl gas (21) (Scheme 1).

Reaction of **3a** with triethyl orthoformate gave the corresponding 2-ethoxymethyleneamino derivative **6**. Hydrazinolysis of **6** in ethanol at room temperature yielded 10--amino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho[2,1-b]pyrano[2,3-d]pyrimidine (**7a**). Aminolysis of **6** with methylamine gave the corresponding 10-methyl-pyranopyrimidine derivative **7b**, and with dimethylamine it gave 2-*N*,*N*-dimethylaminomethylene derivative **8**. Ammonolysis of **6** gave 11-amino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]pyrimidine **10**. Also, the structure of **10** was established on the basis of IR, which showed the absence of CN and showed signals due to –CH pyrimidine. Also, the structure of compound **10** was established by an independent synthesis from **3a** and formamide (m.p. and mixed m.p.) (Scheme 2). Condensation of **6** with H_2S yielded a product that was identified as 10,11-dihydro-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho-[2,1-b]pyrano[2,3-d]pyrimidine-11-thione (**9**). Treatment of **7a** with acetyl and/or benzoyl chloride gave the corresponding 11-methoxy-2-methyl/phenyl-14-(*p*-tolyl)-14*H*-naphtho[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**11b**,**c**), while cyclocondensation of **7a** with ethyl cyanoacetate or diethyl oxalate gave the corresponding 2-cyanomethyl and 2-ethoxycarbonyl derivatives (**11d**,**e**). Also, **7a** reacted with triethyl orthoformate to afford the corresponding [1,2,4]triazolo[1,5-c]pyrimidine derivative (**11a**), while the reaction of **7a** with benzaldehyde gave 10-benzalamino-10,11dihydro-11-imino-3-methoxy-12--(*p*-tolyl)12*H*-naphtho[2,1-b]pyrano[2,3-d]pyrimidine (**12**) instead of the expected triazolopyrimidine derivative (**11c**). Treatment of **7a** with two moles of ethyl chloroformate in dry benzene afforded 1:2 adduct **13** (Scheme 2). Formation of **13** was assumed to proceed via bis(ethoxycarbonyl) derivative **A** as intermediate, which cyclized into **13** with elimination of ethanol (Scheme 2).

On the other hand, when 2-cyanomethylderivative **11d** was subjected to the reaction with phenolic aldehydes, a condensation reaction afforded new pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives (**14a**,**b**) containing the coumarin moiety (Scheme 3).



Scheme 3

The present study revealed that substitution at the 2-position of pyrano[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine with coumarin-3-yl and/or benzocoumarin-3-yl moieties (compounds **14a,b**) caused a pronounced increase in their activities.

It was found that compounds **14a,b** possess a pronounced antimicrobial activity against all tested microorganisms, namely, markedly stronger antimicrobial activity against both Gram-positive and Gram-negative bacteria than ampicillin. Compounds **5b** and **11b,d** exhibited stronger activities than ampicillin also towards *Staphylococcus aureus*, compounds **11b,c** towards *Bacillus cereus*, compounds **11b-e** and **13** posses pronounced activities towards *Bacillus subtilis.* Compounds **7b, 10** and **11c-e** exhibited pronounced activities against *Serratia marcescens* and compounds **11a,c,d** and **13** demonstrated interesting activities against *Proteus mirabilis*. Also, compounds **5a,b, 7a,b, 9, 10, 11a-e** and **13** exhibited pronounced activities towards *Escherichia coli.* Compounds **11a,c** and **13** exhibited equal activities as ampicillin towards *Staphylococcus aureus*, compounds **5b** and **11e** the same activities towards *Bacillus cereus*, compounds **5b, 9** and **11a** also the same effect against *Bacillus subtilis*. Compound **13** showed the same effect towards *Serratia marcescens* and *Escherichia coli*, while compound **11b** similar activities towards *Proteus mirabilis* compared with ampicillin.

In general as far as Gram negative bacteria are concerned compounds **5a**,**b**, **7a**,**b**, **10**, **11a**,**c-e**, **13**, **14a**,**b** were found more efficient than ampicillin. The same applies to compounds **11b**,**c**,**d**, **13**, **14a**,**b** in the case of Gram positive bacteria.

The remaining compounds differed in their ability to inhibit the growth of microorganisms in dependence on their chemical structure and are all less effective than ampicillin.

CONCLUSIONS

Evaluation of new compounds established that **5a,b**, **11a-e**, **13** and **14a,b** showed improved antimicrobial activity compared to ampicillin, while compounds **3a-f, 4a,b, 6** and **8** were either inactive or weakly active against the tested microorganisms. We attempted to increase antimicrobial activities by fusing the triazolopyrimidine nucleus with the pyrane ring. The most active compounds were in which the pyranotriazolopyrimidine nucleus was substituted with the coumarin nucleus (compounds **14a,b**).

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S A Ž E T A K

Sinteza i antimikrobno djelovanje derivata nafto[2,1-b]pirano[2,3-d]pirimidina i pirano[3,2-e][1,2,4]triazolo[1,5-c]pirimidina

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Sintetizirano je nekoliko novih nafto[2,1-b]pirano[2,3-d]pirimidina, pirano[3,2-e][1,2,4]-triazolo[1,5-c]pirimidina i njihovih kumarin-3-il derivata. Neki od njih imaju izraženo antimikrobno djelovanje.

Ključne riječi: derivati piranopirimidina, derivati piranotriazolopirimidina, derivati kumarin-3-il-piranotriazolopirimidina, antibakterijsko djelovanje

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