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Synthesis and antimicrobial screening of some fused heterocyclic pyrroles

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Pyrrole derivatives **1a,b** were used as precursors for the preparation of pyrrolo[2,3-*d*]pyrimidine derivatives **2a,b** –**7a,b**. Also, the formation and structure of different pyrrolotriazolopyrimidine derivatives **8a,b**–**11a,b** were discussed. Some of the prepared products showed potent antimicrobial activity.

Keywords: pyrrole, pyrrolo[2,3-*d*]pyrimidine, pyrrolotriazolopyrimidine, antimicrobial activity

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In the last few decades, the chemistry of pyrrole and fused heterocyclic pyrrole derivatives has received considerable attention owing to their synthetic and effective biological importance (1–3). Due to the presence of pyrrolo[2,3-*d*]pyrimidine moiety in some important antibiotics (4, 5) and because of their structural resemblance to purines, interest has arisen in the construction of such molecules. On the other hand, the thermal rearrangement of isomeric triazoles to their thermodynamically more stable isomers has rarely been discussed in di- and triheterocycles (6–8).

The possibility of formation of isomeric triazolopyrimidines has been overlooked in many reports (9–11). However, it was taken into consideration in the reaction of some 4-hydrazinopyrimidines with one carbon donor moiety, yielding the respective isomeric triazolopyrimidines (6–8, 12–16). So far, isomeric conversion of pyrrolotriazolopyrimidines was rarely reported (17). These findings encouraged us to undertake the synthesis of some new pyrrolo[2,3-*d*]pyrimidine and fused pyrrolo[2,3-*d*]pyrimidine derivatives hoping that they could be of promising chemical and biological interest.

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EXPERIMENTAL

All melting points were uncorrected and measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Microanalytical data were performed by Vario, Elementar apparatus (Shimadzu). The IR spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrophotometer (USA). ^{1}H NMR spectra were determined on a Varian Mercury (300 MHz) spectrometer (Varian, UK) in $CDCl_3$ and the chemical shifts were expressed in ppm relative to TMS as internal reference. Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu).

Physicochemical and spectral data for the synthesised compounds are given in Tables I and II.

Syntheses of compounds **1a, 2a** and **3a** were performed according to ref. 18.

*Synthesis of 2-amino-1-(3,4-dichlorophenyl)-4-phenyl-1*H*-pyrrole-3-carbonitrile* (**1b**)

To a solution of phenacyl bromide (2 g, 0.01 mol), 3,4-dichloroaniline (1.62 g, 0.01 mol) in ethanol (20 mL) and a saturated solution of sodium bicarbonate (5 mL) were added. The reaction mixture was kept at 70 °C for 1 h, cooled, poured into cold water, filtered off, dried. The obtained product was dissolved in an appropriate amount of ethanol (20 mL) and then malononitrile (0.66 g, 0.01 mol) was added portionwise, followed by sodium ethoxide (0.01 mol) and left to reflux till a solid was formed. Solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **1b**.

*Synthesis of 7-(3,4-dichlorophenyl)-3,7-dihydro-5-phenyl-7*H*-pyrrolo[2,3-d]pyrimidin--4-one* (**2b**)

Compound **1b** (0.01 mol) in formic acid (20 mL, 85%) was refluxed for 3 h, cooled, poured onto ice-water to give a precipitate, which was filtered off, dried and recrystallized from ethanol to afford **2b**.

*Synthesis of 4-chloro-7-(3,4-dichlorophenyl)-5-phenyl-7*H*-pyrrolo[2,3-d]pyrimidine* (**3b**)

Compound **2b** (0.01 mol) was refluxed in phosphorus oxychloride (30 mL) for 3 h, cooled, poured onto ice-water to give a precipitate, which was filtered off, dried and recrystallized from ethanol to afford **3b**.

*Synthesis of (6,7-disubstituted-5-phenyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine* (**4a,b**)

Method A. – A mixture of **3a** or **3b** (0.01 mol) and hydrazine hydrate (5 mL, 98%) was refluxed in absolute ethanol (20 mL) for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **4a** and **4b**.

Method B. – To a mixture of **5a** or **5b** (0.01 mol) in dry benzene (20 mL), hydrazine hydrate (5 mL, 98%) was added under stirring at room temperature for 4 h. The solvent

Table I. Elemental analysis of the newly prepared compounds

Compd. No.	Yield (%)	M. p. (°C)	Mol. formula (M_r)	Found/calcd. (%)				
				C	H	N	Cl	S
1b	36	196–198	$C_{17}H_{11}Cl_2N_3$	62.34	3.32	12.67	21.64	
			(328.20)	62.21	3.38	12.80	21.60	
2b	60	285–287	$C_{18}H_{11}Cl_2N_3O$	60.38	3.18	11.94	20.02	
			(356.21)	60.69	3.11	11.80	19.91	
3b	30	168–170	$C_{18}H_{10}Cl_3N_3$	57.60	2.80	11.29	28.24	
			(374.66)	57.71	2.69	11.22	28.39	
4a	76	185–187	$C_{25}H_{21}N_5$	76.43	5.84	17.71		
			(391.48)	6.317	5.89	17.80		
4b	65	253–255	$C_{18}H_{13}Cl_2N_5$	58.32	3.48	19.15	18.95	
			(370.24)	58.39	3.54	18.92	18.92	
5a	85	163–165	$C_{27}H_{23}N_3O$	79.94	5.69	10.39		
			(405.50)	79.97	5.72	10.36		
5b	60	190–192	$C_{20}H_{15}Cl_2N_3O$	62.45	4.02	10.92	18.40	
			(384.27)	62.51	3.93	10.94	18.45	
6a	A: 80	182–184	$C_{25}H_{20}N_4$	79.74	5.24	14.94		
	B: 76		(376.46)	79.76	5.35	14.88		
6b	A: 75	188–190	$C_{18}H_{12}Cl_2N_4$	60.72	3.49	15.68	20.07	
	B: 65		(355.23)	60.86	3.41	15.77	19.96	
7a	70	170–172	$C_{26}H_{22}N_4$	79.86	5.56	14.54		
			(390.49)	79.97	5.68	14.35		
7b	60	186–188	$C_{19}H_{14}Cl_2N_4$	61.87	3.84	15.09	19.10	
			(369.26)	61.80	3.82	15.17	19.20	
8a	A: 85	176–178	$C_{26}H_{19}N_5$	77.49	5.27	17.14		
	B: 66		(401.47)	77.40	5.25	17.36		
8b	60	192–194	$C_{19}H_{11}Cl_2N_5$	59.70	3.34	18.32	18.55	
			(380.24)	60.02	2.92	18.42	18.65	
9a	85	188–190	$C_{27}H_{21}N_5$	78.12	4.99	16.88		
			(415.50)	78.05	5.09	16.86		
9b	60	213–215	$C_{20}H_{13}Cl_2N_5$	60.80	3.41	17.67	18.09	
			(394.27)	60.93	3.32	17.76	17.98	
10a	76	245–247	$C_{32}H_{23}N_5$	80.43	4.88	14.61		
			(477.57)	80.48	4.85	14.66		
10b	80	281–283	$C_{25}H_{15}Cl_2N_5$	65.51	3.44	15.28	15.67	
			(456.34)	65.80	3.31	15.35	15.54	
11a	76	136–138	$C_{26}H_{19}N_5S$	72.25	4.33	16.04		7.36
			(433.54)	72.03	4.42	16.15		7.40
11b	76	150–152	$C_{19}H_{11}Cl_2N_5S$	55.18	2.66	16.84	17.41	7.84
			(412.30)	55.35	2.69	16.99	17.20	7.78

was removed under reduced pressure, and the residues were recrystallized from methanol to give **4a** and **4b**. Compounds **4a** and **4b** prepared by this method are identical in all respects (physical and spectral data) to those prepared by method A.

Table II. Spectral data of the newly prepared compounds

Compd. No.	Mass (*m*/*z*)	IR (ν, cm^{-1})	^1H NMR (δ, ppm)
1b	331[M+4](12) 329 [M+2](65) 327 [M^+](100)	3430, 3330 (NH_2) 2210 (CN)	4.20 (brs, 2H, NH_2, D_2O exchangeable), 6.8–7.5 (m, 8H, Ar-H), 7.9 (s, 1H, C_5-H)
2b	359 [M+4](12) 357 [M+2](64) 355 [M^+](100)	3130 (NH) 1682 (CO) 1587 (C=N)	7.2–7.9 (m, 8H, Ar-H), 8.1 (s, 1H, C_6-H), 8.3 (s, 1H, C_2-H), 12.20 (s, 1H, NH, D_2O exchangeable)
3b	373 [M^+](100) 375 [M+2](90) 377 [M+4](35) 379 [M+6](5)	1580 (C=N)	7.24–7.95 (m, 8H, Ar-H), 8.2 (s, 1H, C_6-H), 8.46 (s, 1H, C_2-H)
4a	391 [M^+](100)	3430, 3330 (NH_2) 3210 (NH)	4.9–5 (brs, 2H, NH_2, D_2O exchangeable), 5.3 (s, 2H, CH_2), 6.9–7.4 (m, 16H, Ar-H, NH, D_2O exchangeable), 8.1 (s, 1H, C_2-H)
4b	373 [M+4](11) 371 [M+2](65) 369 [M^+](100)	3430, 3330 (NH_2) 3230 (NH)	4.8–4.9 (brs, 2H, NH_2, D_2O exchangeable), 7.1–7.6 (m, 9H, Ar-H, NH, D_2O exchangeable), 7.8 (s, 1H, C_6-H), 8.1 (s, 1H, C_2-H)
5a	405 [M^+](90)	2210 (CN) 1560 (C=N)	1.30 (t, 3H, CH_3), 2.40 (q, 2H, CH_2), 5.10 (s, 2H, CH_2), 6.8–7.5 (m, 16H, N=CH, Ar-H)
5b	375 [M+4](11) 373 [M+2](65) 371 [M^+](100)	2250 (CN) 1540 (C=N)	1.32 (t, 3H, CH_3), 2.50 (q, 2H, CH_2), 6.8–7.6 (m, 9H, N=CH, Ar-H), 7.9 (s, 1H, C_5-H)
6a	376 [M^+](100)	3430, 3330 (NH_2)	4.9–5.0 (brs, 2H, NH_2, D_2O exchangeable), 5.35 (s, 2H, CH_2), 6.8–7.3 (m, 15H, Ar-H), 8.4 (s, 1H, C_2-H)
6b	358 [M+4](11) 356 [M+2](65) 354 [M^+](100)	3430, 3330 (NH_2)	6.1–6.2 (brs, 2H, NH_2, D_2O exchangeable), 7.4–7.9 (m, 8H, Ar-H), 8.2 (s, 1H, C_6-H), 8.4 (s, 1H, C_2-H)
7a	390 [M^+](100)	3250 (NH)	2.6 (s, 3H, CH_3), 5.3 (s, 2H, CH_2), 6.8–7.5 (m, 16H, Ar-H, NH, D_2O exchangeable), 8.2 (s, 1H, C_2-H)
7b	372 [M+4](11) 370[M+2](65) 368 [M^+](100)	3265 (NH)	2.6 (s, 3H, CH_3), 6.8–7.5 (m, 9H, Ar-H, NH, D_2O exchangeable), 7.8 (s, 1H, C_6-H), 8.2 (s, 1H, C_2-H)
8a	401 [M^+](100)	3090, 2890 (CH) 1580 (C=N)	5.5 (s, 2H, CH_2), 6.8–7.5 (m, 15H, Ar-H), 8.3 (s, 1H, C_2-H), 9.1 (s, 1H, C_5-H)
8b	386 [M+4](11) 384 [M+2](65) 382 [M^+](100)	3100, 2900 (CH) 1580 (C=N)	6.8–7.5 (m, 8H, Ar-H), 7.8 (s, 1H, C_8-H), 8.2 (s, 1H, C_2-H), 9.2 (s, 1H, C_5-H)
9a	415 [M^+](100)	3060, 2870 (CH) 1520 (C=N) 1630 (C=C)	2.6 (s, 3H, C_2-CH_3), 5.5 (s, 2H, CH_2), 6.9–7.5 (m, 15H, Ar-H), 9.05 (s, 1H, C_5-H)

Table II. continued

Compd. No.	Mass (*m*/*z*)	IR (ν, cm^{-1})	^1H NMR (δ, ppm)
9b	398 [M+4](11), 396 [M+2](65), 394 [M^+](100)	3090, 2880 (CH) 1560 (C=N)	2.7 (s, 3H, C_2-CH_3), 6.8–7.5 (m, 8H, Ar-H), 7.8 (s, 1H, C_8-H), 9.3 (s, 1H, C_5-H)
10a	477 [M^+](100)	1520 (C=N)	5.55 (s, 2H, CH_2), 6.8–7.6 (m, 20H, Ar-H), 9.2 (s, 1H, C_5-H)
10b	459 [M+4](11), 457 [M+2](65), 455 [M^+](100)	1580 (C=N)	6.8–7.5 (m, 13H, Ar-H), 7.9 (s, 1H, C_8-H), 9.4 (s, 1H, C_5-H)
11a	376 [M^+–NCS] (100)	1580 (C=N)	3.9–4.2 (brs, 1H, SH, D_2O exchangeable), 5.4 (s, 2H, CH_2), 6.8–7.5 (m, 15H, Ar-H), 8.5 (s, 1H, C_5-H)
11b	357 [M+4–NCS] (11) 355 [M+2–NCS](65) 353 [M^+–NSC] (100)	1580 (C=N)	4.1–4.3 (brs, 1H, SH, D_2O exchangeable), 6.8–7.5 (m, 8 H, Ar-H), 7.9 (s, 1H, C_8-H), 8.6 (s, 1H, C_5-H)

*Synthesis of 2-ethoxymethylenamino-1,5-disubstituted-4-phenyl-1*H*-pyrrole-3-carbonitrile* (**5a,b**)

Compounds **1a** or **1b** (0.01 mol) were refluxed in triethyl orthoformate (20 mL) for 6 h. The solvent was removed under reduced pressure to give **5a** or **5b**.

*Synthesis of 6,7-disubstituted-5-phenyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-ylamine* (**6a**,**b**)

Method A. – A mixture of **1a** or **1b** (0.01 mol) and formamide (30 mL) was heated at 110 °C for 3 h, cooled, poured onto ice-water to give precipitates, which were filtered off, dried, and recrystallized from ethanol to afford **6a** or **6b**.

Method B. – To a solution of compound **5a** or **5b** (0.01 mol) in dry ethanol (20 mL), ammonium hydroxide solution (5 mL, 25%) was added under stirring at 0 °C for 30 min, then at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **6a** or **6b**. Compounds **6a** and **6b** prepared by this method are identical in all respects (physical and spectral data) to those prepared by method A.

*Synthesis of (6,7-disubstituted-5-phenyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-methylamine* (**7a,b**)

To a solution of **5a** or **5b** (0.01 mol) in dry ethanol (20 mL), methylamine solution (5 mL) was added under stirring at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **7a** or **7b**.

*Synthesis of 7,8-disubstituted-9-phenyl-7*H*-pyrrolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine* (**8a,b**)

Method A. – A mixture of **4a** or **4b** (0.01 mol) and triethyl orthoformate (20 mL) was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **8a** or **8b**.

Method B. – Compound **4a** or **4b** (0.01 mol) was refluxed in formic acid (20 mL, 85%) for 5 h, cooled, and poured onto ice-water. The precipitate was filtered off, left to dry and then recrystallized from ethanol to afford **8a** or **8b**. Compounds **8a** and **8b** prepared by this method are identical in all respects (physical and spectral data) to those prepared by method A.

*Synthesis of 7,8-disubstituted-2-methyl-9-phenyl-7*H*-pyrrolo[4,3-e][1,2,4]triazolo[1,5-c]-pyrimidine* (**9a,b**)

Method A. – A mixture of **4a** or **4b** (0.01 mol) and triethyl orthoacetate (20 mL) was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **9a** or **9b**.

Method B. – A mixture of **4a** or **4b** (0.01 mol), acetic anhydride (20 mL), and acetic acid (10 mL) was refluxed for 5 h, cooled, and poured onto ice-water. The precipitate was filtered off, left to dry and then recrystallized from ethanol to give **9a** or **9b**. Compounds **9a** and **9b** prepared by this method are identical in all respects (physical and spectral data) to those prepared by method A.

*Synthesis of 7,8-disubstituted-2,9-diphenyl-7*H*-pyrrolo[4,3-e][1,2,4]triazolo[1,5-c]-pyrimidine* (**10a,b**)

A mixture of **4a** or **4b** (0.01 mol), benzoyl chloride (5 mL) and trimethylamine (0.5 mL) was refluxed in dry ethanol (20 mL) for 6 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give **10a** or **10b**.

*Synthesis of 7,8-disubstituted-2-mercapto-9-phenyl-7*H*-pyrrolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidine (***11a,b***)*

To an aqueous solution of **4a** or **4b** (0.01 mol) in ethanol (20 mL), carbon disulfide (10 mL) was added, then the reaction mixture was refluxed on a water-bath for 3 h, cooled, poured onto ice-water, and neutralized with 2–3 drops of hydrochloric acid (35%). The precipitate was filtered off, left to dry and recrystallized from methanol to give **11a** or **11b**.

Antimicrobial activity

The *in vitro* antimicrobial activity of the synthesized compounds was investigated against several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus* ATCC 29231, *Bacillus subtilis* ATCC 10783, *Mycobacterium phlei* ATCC 1014, *Streptococcus*

Table III. Test of the synthesized compounds

Compounds[a]	Disc diffusion test (mm)					
	E. coli ATCCC 11105	*S. aureus* ATCCC 29231	*M. phlei* ATCCC 10142	*S. pyogenes* ATCCC 10782	*C. albicans* ATCCC 10231	*B. subtilis* ATCCC 10783
Amoxicillin[b]	10	–	–	–	–	13
Nystatin[c]	–	–	–	–	20	–
1b	–	–	–	–	–	7
2a	–	11	19	23	–	16
4b	–	–	–	–	13	11
6a	–	–	10	5	–	8
6b	–	–	–	–	–	8
8a	–	–	–	–	–	9
9a	–	–	–	–	–	–

[a] γ = 2 μg mL^{-1} in DMSO
[b] γ = 25 μg mL^{-1}
[c] γ = 4 μg mL^{-1}

pyogenes ATCC 10782), Gram-negative bacteria (*Escherichia coli* ATCC 11105) and yeast (*Candida albicans* ATCC 10231). All microorganisms used were obtained from the culture collection of the Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University, Cairo, Egypt. Compounds were tested against *Escherichia coli* and *Staphylococcus aureus* in a nutrient broth, pH = 7.0, against *Bacillus subtilis, Mycobacterium phlei* and *Streptococcus pyogenes* in the Bacto brain heart infusion broth, pH = 7.0, and against *Candida albicans* in a broth containing 1% peptone, 2% dextrose, pH = 5.7. *Escherichia coli* of known antibiotic sensitivity served for control purposes.

Media for disc sensitivity tests were the nutrient agar and Muller-Hinton agar (MHA) purchased from Difco (USA). Nonsterile powder of the tested compound was dissolved in sterile DMSO to yield 2.0 μg mL^{-1}, and passed through 0.2 μm membrane filter (Millipore Corp, USA). The filtrates were dispensed as 2 mL samples into sterile, small screw--capped vials, frosen and kept stored at –15 °C. The vials were refrozen after thawing.

Disc diffusion sensitivity test was done in the manner identical to that of Bauer *et al*. (19). DMSO showed no inhibition zones. Amoxicilin (Bioanalyse, Turkey) and nystatin (Sigma – Aldrich, USA) were used as reference substances.

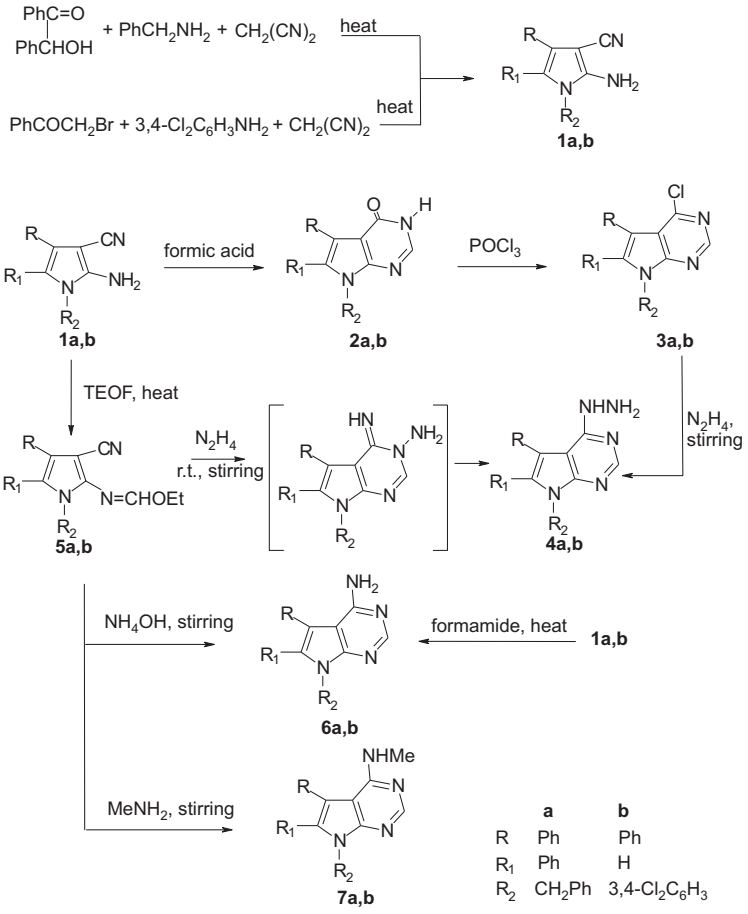
RESULTS AND DISCUSSION

2-Amino-1*H*-pyrrole-3-carbonitrile derivatives **1a** and **1b** were used as key compounds for this study and for syntheses of other fused heterocycles. Derivatives **1a-3a** were prepared as reported previously (18), while compound **1b** was prepared by refluxing a mixture of phenacyl bromide, 3,4-dichloroaniline, and malononitrile in dry ethanol. The structure of compound **1b** was confirmed by spectral data (Table II). The synthesis of pyrrolo[2,3-*d*]pyrimidin-4-one derivative **2b** was achieved by refluxing compound **1b**

with formic acid. The IR spectrum of the latter compound showed the absence of cyano group and the presence of CO and NH groups. Its ^{1}H NMR spectrum in $CDCl_3$ revealed a signal at (δ, ppm): 12.20 (s, 1H, NH, exchangeable with D_2O) (Table II). The latter compound was converted to its corresponding 4-chloro derivative **3b** by refluxing with phosphorus oxychloride; its MS gave the characteristic fragmentation pattern due to the presence of three chlorine atoms (Table II).

Pyrrolo[2,3-*d*]pyrimidin-4-yl)-hydrazine derivatives **4a,b** were obtained from derivatives **3a,b** by heating with hydrazine hydrate (Scheme 1). The ^{1}H NMR spectra of compounds **4a,b** revealed signals characteristic of NH_2 and NH, and their MS gave the molecular ion peak as a base peak (Table II).

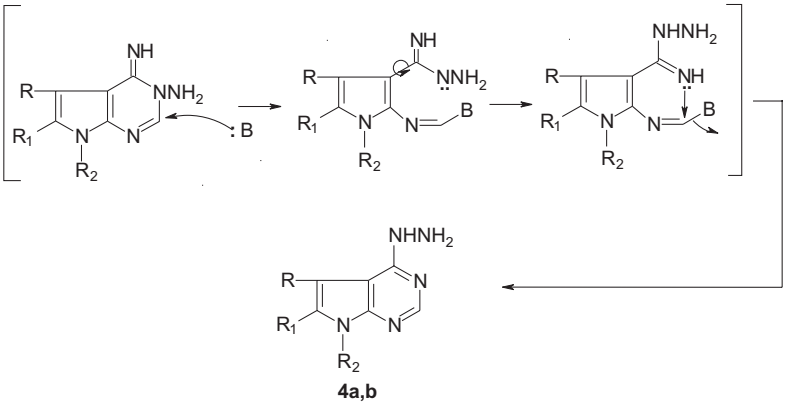
On the other hand, when the pyrrole derivatives **1a,b** were refluxed with triethyl orthoformate, they afforded the corresponding 2-ethoxymethyleneamino derivatives **5a,b** (Scheme 1). The spectral data of compounds **5a,b** confirmed their structures (Table II).



Scheme 1

Many reports (17, 18, 20) stated that hydrazinolysis of compounds analogous to **5a,b**, in polar solvents, gave the respective imino derivatives that could be isolated and identified. However, our attempts to cyclize compounds **5a,b** by stirring with hydrazine hydrate in dry ethanol gave compounds **1a,b**. Surprisingly, using a nonpolar solvent (dry benzene), compounds **4a,b** were obtained directly without isolation of the imino derivatives. This could be explained by the formation of the imino derivatives first, which in the presence of a base (excess hydrazine hydrate) underwent a Dimroth rearrangement to give the thermodynamically more stable derivatives **4a,b** (8) (Scheme 2).

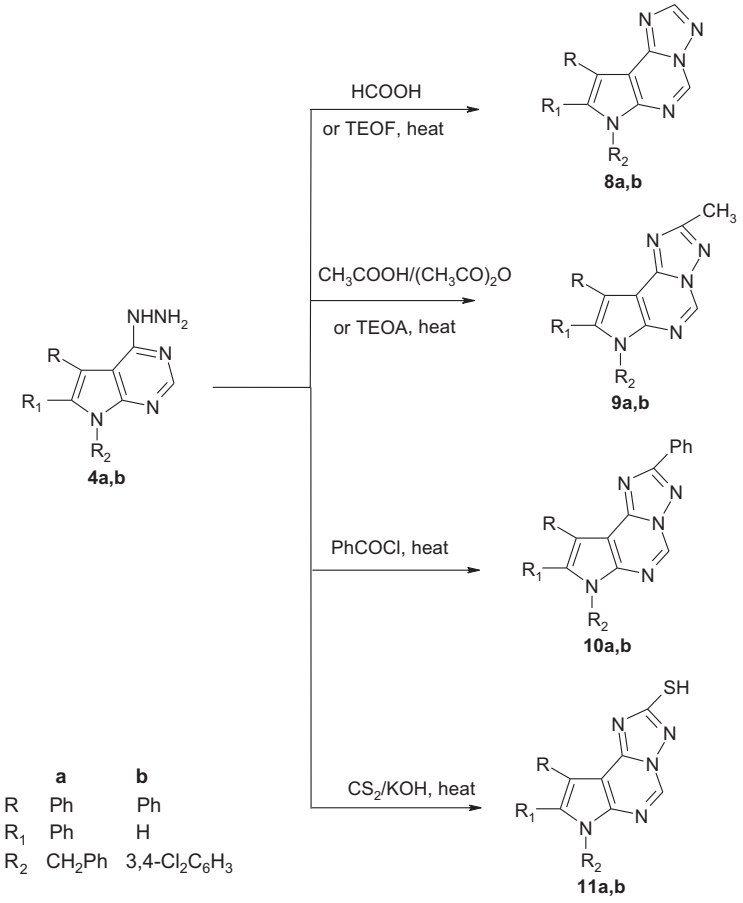
When compounds **1a,b** were heated with formamide or compounds **5a,b** were stirred with ammonium hydroxide solution they afforded pyrrolo[2,3-*d*]pyrimidin-4-ylamine derivatives **6a,b**, respectively. Also, when compounds **1a,b** were stirred with methylamine solution, they gave pyrrolo[2,3-*d*]pyrimidin-4-yl)-methylamine derivatives **7a,b**, respectively (Scheme 1). The IR and ^{1}H NMR spectra of the aforementioned compounds revealed the absence of the cyano group and the presence of NH_2 in compounds **6a,b** and NH in compounds **7a,b** (Table II).



	a	b
R	Ph	Ph
R_1	Ph	H
R_2	CH_2Ph	3,4-$Cl_2C_6H_3$

Scheme 2

Previous observations revealed that [1,2,4]triazolo[4,3-*c*]pyrimidines can isomerize under different suitable reaction conditions to the thermodynamically more stable [1,2,4]-triazolo[1,5-*c*]pyrimidines (6, 8, 17). This isomerization was reported early by Miller *et al*. (21, 22) when they treated [1,2,4]triazolo[4,3-*c*]pyrimidine derivatives with an acid, base, or thermally. In this investigation, and in continuation of our previous work (8, 23), in the synthesis of different fused triazolopyrimidines, refluxing of compounds **4a,b** with formic acid or triethyl orthoformate (TEOF), acetic acid/acetic anhydride or triethyl orthoacetate (TEOA), gave one and the same product assigned to the structures of 7,8--disubstituted-pyrrolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **8a,b** and **9a,b**, respectively (Scheme 3, Table II). Similarly, on refluxing compounds **4a,b** with benzoyl chloride or carbon disulfide, 7,8-disubstituted-2,9-diphenyl-7*H*-pyrrolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidines **10a,b** or 7,8-disubstituted-2-mercapto-9-phenyl-7*H*-pyrrolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives **11a,b** were obtained, respectively (Scheme 3).



Scheme 3

In fact, the triazolo[4,3-*c*]pyrimidine derivatives could not be isolated even when the reaction mixture was heated at a low temperature (40–60 °C) and for a short time. TLC monitoring revealed the formation of more than one spot during the reaction, which ended in formation of the final product. This could be explained by the formation of the triazolo[4,3-*c*]pyrimidine derivatives first, which on heating (24) or in the presence of an acid (8, 17, 21) or base (6, 8, 21) rearranged to the thermodynamically more stable form of triazolo[1,5-*c*]pyrimidine derivatives through a series of ring opening and ring closure reactions (Scheme 2).

The antimicrobial activity of some newly synthesized compounds, 2-amino-1*H*-pyrrole-3-carbonitrile, **1b**, pyrrolo[2,3-*d*]pyrimidin-4-one derivative, **2a**, pyrrolo[2,3-*d*]pyrimidin-4-yl)-hydrazine derivative, **4b**, pyrrolo[2,3-*d*]pyrimidin-4-ylamine derivatives **6a**, and **6b**, 7,8-disubstituted-pyrrolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **8a** and **9a** was tested and the results are shown in Table III. It was noticed that compound **2a** demonstrated the highest inhibitory activity of all the tested compounds and the reference drug. On the other hand, it was found that compounds **2a, 4b,** and **6a** revealed antibacterial activity more effective than the reference drug. In general, it is obvious that compounds of series **a** (substituted benzyl) were more effective than those of series **b** (substituted dichlorophenyl). The promising antimicrobial activity of pyrrolo[2,3-*d*]pyrimidine derivatives prompted us to add another heterocyclic ring (the triazole ring) hoping that it would increase the activity, but unfortunately the activity decreased.

CONCLUSIONS

Evaluation of the new compounds established that pyrrolo[2,3-*d*]pyrimidin-4-one derivative, **2a**, showed improved antimicrobial activity compared to amoxicillin, while the other compounds, pyrrolo[2,3-*d*]pyrimidin-4-yl)-hydrazine derivative, **4b**, pyrrolo[2,3-*d*]pyrimidin-4-ylamine derivatives **6a** and **6b** were weakly active against the tested microorganisms.

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REFERENCES

1. G. Baccolini and C. Sandali, Synthesis of pyrroles under mild conditions using PCl_3, ketones and alkylhydrazines, *J. Chem. Soc. Chem. Commun.* **1987**, 788–789.
2. E. Toja, A. Depaoli, G. Tuan and J. Kettenring, Synthesis of 2-amino-3-ethoxycarbonylpyrroles, *Synthesis* **1987**, 272–274.

3. K. A. M. El-Bayouki, W. M. Basyouni, H. Hosni and A. Shehab El-Deen, Pyrrolo[2,3-*d*]pyrimidines. Part 1. Synthesis of novel pyrrolo[2,3-*d*]pyrimidine derivatives with antimicrobial activity, *J. Chem. Res. (S)* **1995**, 314–315.
4. Y. Misumo, M. J. Ikehara, K. A. Watanabe, S. Suzuki and T. Itoh, Synthetic studies of potential antimetabolites. IX. The anomeric configuration of tubercidin, *J. Org. Chem.* **28** (1969) 3329–3331.
5. K. V. Rao, Structure of sangivamycin, *J. Med. Chem.* **11** (1968) 939–941.
6. C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan and V. S. Bhadti, Studies in the synthesis and interconversion of isomeric triazolothienopyrimidines, *J. Heterocycl. Chem.* **18** (1981) 43–46.
7. A. R. Katritski, Ji Fu-Bao, W. Fan, J. K. Gollas, J. V. Greenhill and R. W. King, Novel dimroth rearrangements of the benzotriazole system: 4-amino-1-(arylsulfonyl)benzotriazoles to 4-[(arylsulfonyl)amino]benzotriazoles**,** *J. Org. Chem.* **57** (1992) 190–195.
8. A. E. Rashad, O. A. Heikal, A. O. H. El-Nezhawy and F. M. E. Abdel-Megeid, Synthesis and isomerization of thienotriazolopyrimidine and thienotetrazolopyrimidine derivatives with potential anti-inflammatory activity, *Heteroat. Chem.* **16** (2005) 226–234.
9. A. M. Abdel-Fattah, A. S. Aly, F. A. Gad, N. A. Hassan and A. B. A. El-Gazzar, A facile synthesis of isoxazolo [5′,4′: 4,5]thiazolo[3,2-*a*]thienopyrimidine, a new ring system, *Phosphorus Sulfur* **141** (1998) 263–281.
10. V. P. Arya, Synthesis of heterocycles: Part VI. Synthesis of novel condensed thiophenes, *Indian J. Chem.* **10** (1972) 1141–1150.
11. A. B. A. El-Gazzar and N. A. Hassan, Synthesis of polynuclear heterocyclic compounds derived from thieno[2,3-*d*]pyrimidine derivatives, *Molecules* **5** (2000) 835–850.
12. K. Kottke and H. Kuehmstedt, Synthesis of compounds with amino guanidine structure, part 5. 1-Methyl-4-aryl-s-triazolo[4,3-*a*]quinazol-5-one, 1,4-diaryl-5-triazolo[4,3-*a*]quinazol-5-one, *Pharmazie* **33** (1978) 507–509.
13. M. E. A. Zaki, Synthesis of novel fused heterocycles based on pyrano[2,3-*c*]pyrazole, *Molecules* **3** (1998) 71–79.
14. A. A. Moneer, M. M. Ismail, A. N. Osman, B. Abdel-Fattah and K. M. Ghoniem, Synthesis of certain thienopyrimidines of anticipated analgesic activity, *Egypt. J. Pharm. Sci.* **34** (1993) 623–641.
15. F. Gatta and M. Luciani, Pyrazolo[3,4-*d*]pyrimidines related to lonidamine, *J. Heterocycl. Chem.* **26** (1988) 613–618.
16. T. Nagamatsu and T. Fujita, The first reliable, general synthesis of 5,6-dihydro-1,2,4-triazolo-[4,3-*c*]pyrimidine and the rates of isomerization of the [4,3-*c*] compounds into their [1,5-*c*] isomers, *Heterocycles* **57** (2002) 631–636.
17. C. G. Dave and R. D. Shah, Synthesis of isomeric triazolopyrrolopyrimidines, *J. Heterocycl. Chem.* **37** (2000) 757–761.
18. P. M. Traxler, P. Furet, H. Mett, E. Buchdunger, T. Meyer and N. Lydon, 4-(Phenylamino)pyrrolopyrimidines: Potent and selective, ATP site directed inhibitors of the EGF-Receptor Protein Tyrosine Kinase, *J. Med. Chem.* **39** (1996) 2285–2290.
19. A. W. Bauer, M. M. Kirby, J. C. Sherris and M. Turck, Antibiotic susceptibility testing by a standardized single disc method, *Am. J. Clin. Pathol.* **45** (1996) 493–496.
20. A. S. Ali, N. M. Fathy, S. A. Swelam and F. M. E. Abdel-Megeid, New derivatives of pyrrolo-[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines, *Egypt. J. Pharm. Sci.* **33** (1992) 473–484.
21. G. W. Miller and F. L. Rose, Synthesis of s-triazolopyrimidine derivatives, *J. Chem. Soc.* **1964**, 5642–5644.
22. G. W. Miller and F. L. Rose; Studies on s-triazolo[2,3-*c*]pyrimidine derivatives, *J. Chem. Soc.* **1965**, 3369–3372.

23. A. H. Shamroukh, A. E. Rashad and H. H. Sayed, Synthesis of some pyrazolo[3,4-*d*]pyrimidine derivatives for biological evaluation, *Phosphorus Sulfu*, **180** (2005) 2347–2360.
24. O. Rousseaux, D. Blondeau and H. Sliwa, Synthesis of new heterocyclic phenols: 8-Hydroxy--s-triazolo[1,5-*c*] and [4,3-*c*]pyrimidines, *Tetrahedron Lett*. **27** (1988) 3127–3128.

S A Ž E T A K

Sinteza i antimikrobno djelovanje fuzioniranih heterocikličkih pirola

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Pirolni derivati **1a,b** uporabljeni su kao prekursori za pripravu derivata pirolo[2,3--*d*]pirimidina **2a,b**–**7a,b**. Raspravljano je i nastajanje struktura različitih derivata pirolotriazolopirimidina **8a,b**–**11a,b**. Neki od sintetiziranih spojeva posjeduju izraženo antimikrobno djelovanje.

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