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SYNTHESIS OF SOME 5-FURFURYL PYRIDO[2,3-d] PYRIMIDINES AND 1-ETHYL-5-FURFURYL PYRIDO[2,3-d] **PYRIMIDINES AS POSSIBLE ANTITUMOR &** ANTICANCER AGENTS

Gajendra Singh^a, Anoop K. Sharma^a, A. K. Mishra^a & L. Prakash^a ^a Department of Chemistry, University of Rajasthan, Jaipur, 302004, India

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SYNTHESIS OF SOME 5-FURFURYL PYRIDO[2,3-d] PYRIMIDINES AND 1-ETHYL-5-FURFURYL PYRIDO[2,3-d] PYRIMIDINES AS POSSIBLE ANTITUMOR & ANTICANCER AGENTS

GAJENDRA SINGH, ANOOP K. SHARMA, A. K. MISHRA and L. PRAKASH^{*}

Department of Chemistry, University of Rajasthan, Jaipur-302004 India

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Synthesis of some novel 5-furfuryl pyrido[2,3-d]pyrimidines was carried out by the condensation of 2-amino-3-cyano-4-furfuryl-6-substituted pyridine with various arylisothiocyanates, thiourea and carbondisulphide. These compounds on treatment with ethylbromide using phase transfer catalyst gave 1-ethyl-5-furfuryl pyrido[2,3-d]pyrimidines. The structure of the compounds has been established by elemental, IR and NMR studies. The compounds thus synthesized were screened for their antimicrobial activity.

Keywords: 5-furfuryl; 1-ethyl-5-furfuryl; thioxo; dithio; aminothio & iminothio pyrido [2,3-d]pyrimidines; ethylation by phase transfer catalysis; IR; NMR and antimicrobial activity

INTRODUCTION

A perusal of the literature on pyrido[2,3-d]pyrimidine nucleus is not only revealing of its medicinal importance as antitumor¹⁻⁴ & anticancer⁵⁻⁸ drugs but also inspires us to synthesize some new pyrido[2,3-d]pyrimidine derivatives.

A recent report by Zhao et al⁹ suggested that pyrido[2,3-d]pyrimidine itself possesses antitumor activity. The anticancer activity of dioxo derivatives of pyrido [2,3-d] pyrimidine was reported by Motoo *et al*¹⁰.

^{*} Corresponding author.

Keeping this in mind 5-furfuryl and 1-ethyl-5-furfuryl substituted thioxo, dithio, aminothio and iminothio pyrido[2,3-d]pyrimidine were synthesized.

RESULT & DISCUSSION

Synthesis

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Chalcone I on treatment with dicyanomethane in the presence of ammonium acetate gave 2-amino-3-cyano-4-furfuryl-6-substituted pyridine II through Michael type condensation. II on hydrolysis with 20% alc KOH solution gave 2-amino-3-carboxamido-4-furfuryl-6-substituted pyridines III. III with appropriate arylisothiocyanates in diphenyl ether gave 5-furfuryl-2-thioxo-3,7-disubstituted pyrido[2,3-d]pyrimidine-4(1H)ones IV. pyrido[2,3-d]pyrimi-4-amino-5-furfuryl-7-substituted Whereas. dine-2(1H)thiones V, 5-furfuryl-7-substituted pyrido [2,3-d]pyrimidine 5-furfuryl-4-imino-3,7-disubstituted 2,4(1H,3H) dithiones VI and pyrido[2,3-d]pyrimidine-2(1H)thiones VII were synthesized by condensation of II with different thiourea, carbondisulfide and arylisothiocyantes respectively. The solution of compounds IV, V and VII in methylcyanide was stirred with bromoethane in 50% NaOH solution using phase transfer catalyst to obtain 1-ethyl-5-furfuryl pyrido [2,3-d]pyrimidine derivatives VIIIa, b & c respectively. (Scheme)

All the synthesized compounds were found to be active against the bacteria S. aureus & E. Coli and fungi, A. flavus, A. niger, C. lunata & F. oxysporium.

SPECTRAL STUDIES

The proposed structures of the synthesized compounds are well supported by the spectroscopic and elemental analysis (Table I).

IR spectra

In the IR spectra of Compound II, a sharp band was observed at 2210–2200 cm⁻¹ indicating the presence of the -C=N moiety. This band completely disappeared in compounds IV, V, VI & VII indicating that cyclization has taken place.

		IABLI	E I Unaracterization da	ata of the com	pounds synt	hesized			
Compd. No	R_{I}	R2	Molecular Fourmula	Yield %	M.P. °C		Elementa % Found	l Analysis l (Calcd.)	
			1 OUT MAN		י ג	U	Н	N	S
IVa	4-NH ₂ C ₆ H ₄	2-OCH ₃ C ₆ H ₄	C ₂₄ H ₁₈ O ₃ N ₄ S	85%	>360*	65.21	4.09	12.63	7.21
						(65.16)	(4.07)	(12.67)	(7.24)
IVb	4-NH ₂ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	$C_{24}H_{18}O_{3}N_{4}S$	82%	>340*	62.19	4.10	12.65	7.20
						(65.16)	(4.07)	(12.67)	(7.24)
IVc	4-0CH ₃ C ₆ H ₄	2-OCH ₃ C ₆ H ₄	$C_{25}H_{19}N_{3}O_{4}S$	84%	>340*	69.69	4.19	9.15	6.97
						(65.64)	(4.16)	(61.6)	(00)
IVd	4-0CH ₃ C ₆ H ₄	4-0CH ₃ C ₆ H ₄	$C_{25}H_{19}N_{3}O_{4}S$	78%	>300*	65.68	4.21	9.13	6.95
						(65.64)	(4.16)	(6.19)	(00)
Va	4-NH ₂ C ₆ H ₄		C ₁₇ H ₁₃ ON ₅ S	70%	162	60.93	3.91	20.83	9.51
						(60.89)	(3.88)	(20.89)	(9.55)
٩N	4-0CH ₃ C ₆ H ₄		$C_{18}H_{14}N_4O_2S$	72%	157	61.76	4.05	15.97	9.11
						(61.71)	(4.00)	(16.00)	(9.14)
Vla	4-NH ₂ C ₆ H ₄	·	$C_{17}H_{12}N_4OS_2$	74%	172	57.99	4.45	15.90	18.13
						(57.95)	(4.41)	(15.91)	(18.18)

TABLE I Characterization data of the compounds synthesized

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Compd.	R,	R,	Molecular	Yield %	M.P.		Elementa % Founc	l Analysis l (Calcd.)	
NO.		1	rourmuia		ر	c	Н	2	S
VIb	4-OCH ₃ C ₆ H ₄		C ₁₈ H ₁₃ N ₃ O ₂ S ₂	78%	274	58.89	3.57	11.41	17.40
						(58.85)	(3.54)	(11.44)	(17.44)
VIIa	4-NH ₂ C ₆ H ₄	2-OCH ₃ C ₆ H ₄	$C_{24}H_{19}N_5O_2S$	%69	214	65.35	4.33	15.83	7.23
						(65.31)	(4.30)	(15.87)	(7.26)
VIIb	4-OCH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	C ₂₅ H ₂₀ N ₄ O ₃ S	72%	158	65.83	4.42	12.25	7.00
						(62.79)	(4.38)	(12.28)	(7.02)
VIII _a	4-OCH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	C ₂₅ H ₁₉ O ₄ N ₃ S	70%	195	66.84	7.79	8.63	6.53
						(66.80)	(7.74)	(8.66)	(09.9)
VIII _b	4-OCH ₃ C ₆ H ₄	•	$C_{20}H_{18}N_4O_2S$	%69	148	63.53	4.79	14.87	8.84
						(63.49)	(4.76)	(14.81)	(8.86)
VIIIc	4-OCFH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	$C_{27}H_{24}N_4O_3S$	72%	691	66.97	4.99	11.52	6.57
						(66.94)	(4.96)	(11.57)	(6.61)

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The streaching vibrations of the -NH₂ group appeared as weak band in the region 3450–3320 cm⁻¹ and bending vibration at 1510–1500 cm⁻¹ in compound II, III. Appearance of a new band at 1680–1670 cm⁻¹ in place of -C=N band, in compound III suggested the hydrolysis of -C=N group of II to CONH₂.

The presence of >C=S bands at 1210–1175 cm⁻¹ and three characteristic bands of -NHCS in the region 1235–1170 cm⁻¹ in compounds **IV**, **V**, **VI & VII** and the characteristic bands of >C=O at 1715–1685 cm⁻¹, -NH₂ at 3410–3300 cm⁻¹and >C=NH bands at 3130–3100 cm⁻¹ confirm the proposed structure of compounds **IV**, **V** and **VII** respectively. The absence of the bands for >C=O, -NH₂ and >C=NH and the presence of the bands for >C=S & -NHCS confirm the structure of **VI**.



SCHEME 1

¹H NMR spectra

In the ¹H NMR spectra -OCH₃ protons appeared as a singlet at δ 3.96–2.69 ppm. All the synthesized compounds gave a complex multiplet for

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the aromatic protons of phenyl and furfuryl groups in the range of δ 6.60 to 7.9 ppm.

The bands for -NH₂ protons were generally merged with the complex multiplet of aromatic protons. The -NH proton appeared at 8.9–9.1 ppm in compounds **IV**, **V**, **VI & VII** and disappeared in the ¹H NMR spectra of **VIII** due to substitution of N-H proton with ethyl group. The N-ethylation was further confirmed by tripalet in the range δ 0.8–1.1 ppm and a quartet in the range of δ 1.2–1.4 ppm in compounds **VIIIa**, **b**, **c**.

Antimicmbial Activity

The compounds IV, V, VI, VII & VIII were screened for their antimicrobial activity following the method of Bauer *et al.*¹¹ The concentration was 100 μ g per disk. Streptomycin and Mycostatin were used as reference while testing antibacterial and antifungal activity respectively.

All the synthesized compounds were found to be active against both the micro organisms. The results are recorded in table-II.

EXPERIMENTAL

Melting points of all the synthesized compounds were determined in an open capillary tube and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 577 grating spectrophotometer and ${}^{l}H$ NMR specta in DMSO- d_{6} on a Jeol FX 90Q(90MHz) spectrophotometer using TMS as internal standard.

Chemical shifts are expressed in δ values. The purity of the compounds was checked by TLC using silica gel "G" as adsorbent and visualization was accomoplished by UV light or with Iodine.

Chalcones were synthesized by the usual methods.

Synthesis of 2-amino-3-cyano-4-furfuryl-6-substituted pyridine (II)

A mixture of an appropriate chalcone I (0.05 mole), malononitrile (0.05 mole) and ammonium acetate (0.4 mole) in ethanol (50 ml) was heated on a water bath for 20–22 hrs. After cooling the contents were poured onto crushed ice with constant stirring to obtain a yellow solid mass. This solid was washed with water and ethanol. The dried crude was recrystallized from DMF-EtOH mixture.

	Esckeriekia coli (8mm)	Staphylococcus aurius (9mm)	Aspergillus niger (10mm)	Aspergillus flavous (10)	Fusarium axysporium (12)	Curvularia lunata (11.9)
IVa	10.0	10.2	9.5	8.0	11.0	8.9
	(1.25)	(1,13)	(0.95)	(0.80)	(0.92)	(0.74)
[Vb	4.9	10.6	11.2	11.0	15.0	9.1
	(0.61)	(1.18)	(1.12)	(1.1)	(1.25)	(0.76)
[Vc	6.0	5.0	8.9	0.6	10.5	7.5
	(0.75)	(0.58)	(0.89)	(06.0)	(0.88)	(0.63)
[Vd	9.5	6.3	9.4	10.1	9.9	8.0
	(1.19)	(0.7)	(0.94)	(1.01)	(0.82)	(0.67)
Va	8.0	0.6	10.5	11.9	13.0	10.0
	(06.0)	(1.00)	(1.05)	(1.19)	(1.08)	(0.84)
۷b	5.2	8.0	9.8	10.8	12.0	12.0
	(0.65)	(0.89)	(0.98)	(1.08)	(1.00)	(101)
VIa	6.00	7.0	11.5	12.0	11.0	11.9
	(0.75)	(0.77)	(1.15)	(1.2)	(0.92)	(1.00)
۷Ib	5.4	8.3	10.7	12.7	10.9	10.9
	(0.67)	(0.92)	(1.07)	(1.27)	(0.91)	(16.0)
VIIa	9.6	00.6	6.2	0.6	6.00	13.8
	(1.20)	(1.00)	(0.62)	(06.0)	(0.50)	(1.14)

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	Esckeriekia coli (8mm)	Staphylococcus aurius (9mm)	Aspergillus niger (10mm)	Aspergillus flavous (10)	Fusarium axysporium (12)	Curvularia lunata (11.9)
VIIb	10.1	10.3	8.63	12.2	8.0	12.3
	(1.26)	(1.14)	(0.86)	(1.22)	(0.68)	(1.03)
VIIIa	8.4	4.7	9.1	7.5	8.3	8.8
	(1.05)	(0.52)	(0.91)	(0.75)	(0.69)	(0.74)
VIIIb	6.5	7.8	5.9	5.9	10.0	0.6
	(0.81)	(0.87)	(0.59)	(0.59)	(0.83)	(0.75)
VIIIc	8.0	8.0	10.1	5.7	10.0	6.11
	(1.00)	(0.89)	(101)	(0.57)	(0.83)	(1.00)
* Activi	ity index = Inhibition a	rea of the sample/Inhibi	ition area of the standard.			

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Synthesis of 2-amino-3-carboxamide-4-furfuryl-6-substituted pyridine (III)

2-Amino-3-cyano-4-furfuryl-6-substituted pyridine II (0.04 mole), KOH (0.7 mole) and ethanol (150 ml) were refluxed for 6–7 hrs. After boiling, the mixture was poured into an excess of ice cold water. The solid thus obtained was washed with water and recrystallized with ethanol.

Synthesis of 5-furfuryl-2-thioxo-3, 7-disubstituted pyrido[2,3-d]pyrimidine-4(1H) -one (IV)

A Mixture of 2-amino-3-carboxamido-4-furfuryl-6-substituted pyridine III (0.001 mole) and the appropriate arylisothiocyanate (0.001 mole) was refluxed in diphenyl ether (15 ml) for 8–9 hrs. The reacton mixture after cooling, was added to cold ethanol and the separated solid was filtered, washed with ethanol and recrystallized from DMF-ethanol mixture.

Synthesis of 4-amino-5-furfuryl-7-substututed pyrido[2,3-d]pyrimidine-2(1H)-thione (V)

A mixture of II (0.01 mole) and thiourea (0.02 mole) was heated on oil bath at $120-130^{\circ}$ C for 2 hrs with constant stirring. The temperature was raised to 180° C and finally the mixture was heated at 200° C for 2 hrs. The product thus obtained was washed with water followed by a saturated aqueous sodiumbicarbonate and finally with cold ethanol and recrystal-lized from DMF-EtOH mixture.

Synthesis of 5-furfuryl-7-substituted pyrido[2,3-d]pyrimidine-2,4[1H,3H]-dithiones (VI)

A mixture of II (0.01 mole) and carbon disulphide (0.04 mole) in 15 ml of pyridine was refluxed on water bath for 10–15 hrs. After cooling the excess of pyridine was removed by distillation under reduced pressure and the residue was washed with water followed by a saturated solution of sodium bicarbonate and, finally with cold ethanol and dried. The dried crude product was recrystallized form DMF-EtOH (1:2) mixture.

Synthesis of 5-furfuryl-4-imino –3, 7-disubstituted pyrido[2,3d] pyrimidine-2(1H)-thiones (VII)

A mixture II (0.01 mole), appropriate arylisothiocyanate (0.01 mole), dioxane (15.0 ml) and pyridine (2.0 ml) was heated under reflux at 150° C for about 20–22 hrs. After cooling, the contents of the flask were poured onto crushed ice with constant stirring to afford a yellow solid mass which was washed with water, aqueous sodiumbicarbonate (5% w/v) and finally with water. The dried, crude mass was recrystallized from glacial acetic acid.

Ethylation by Phase transfer catalysis of IV, V & VII

The compounds IV, V & VII (0.01 mole) have been stirred with bromoethane (0.01 mole) in 50% NaOH solution using tetrabutyl ammonium bromide (0.0005 mole) as phase transfer catalyst in methyl cyanide (20 ml) for 4-5 hr.

After neutralization the methyl cyanide layer was separated. The aqueous layer was further extracted with methyl cyanide. The solvent was removed by distillation. The residue was recrystallised from DMF-ethanol mixture to give **VIIIa**, **b** and **c**.

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