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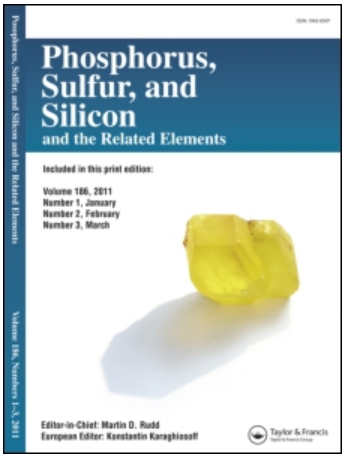


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# SYNTHESIS OF SOME 5-FURFURYL PYRIDO[2,3-*d*] PYRIMIDINES AND 1-ETHYL-5-FURFURYL PYRIDO[2,3-*d*] PYRIMIDINES AS POSSIBLE ANTITUMOR & ANTICANCER AGENTS

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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

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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 antitumor[1–4] & anticancer[5–8] drugs but also inspires us to synthesize some new pyrido[2,3-d]pyrimidine derivatives.

A recent report by Zhao et al[9] 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

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**. Whereas, 4-amino-5-furfuryl-7-substituted pyrido[2,3-d]pyrimidine-2(*1H*)thiones **V**, 5-furfuryl-7-substituted pyrido [2,3-d]pyrimidine 2,4(*1H,3H*)dithiones **VI** and 5-furfuryl-4-imino-3,7-disubstituted 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.

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TABLE I Characterization data of the compounds synthesized

| *Compd. No.* | $R_1$ | $R_2$ | *Molecular Fourmula* | *Yield %* | *M.P. °C* | *Elemental Analysis % Found (Calcd.)* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *C* | *H* | *N* | *S* |
| IVa | 4-$NH_2C_6H_4$ | 2-$OCH_3C_6H_4$ | $C_{24}H_{18}O_3N_4S$ | 85% | >360* | 65.21 | 4.09 | 12.63 | 7.21 |
| | | | | | | (65.16) | (4.07) | (12.67) | (7.24) |
| IVb | 4-$NH_2C_6H_4$ | 4-$OCH_3C_6H_4$ | $C_{24}H_{18}O_3N_4S$ | 82% | >340* | 65.19 | 4.10 | 12.65 | 7.20 |
| | | | | | | (65.16) | (4.07) | (12.67) | (7.24) |
| IVc | 4-$OCH_3C_6H_4$ | 2-$OCH_3C_6H_4$ | $C_{25}H_{19}N_3O_4S$ | 84% | >340* | 65.69 | 4.19 | 9.15 | 6.97 |
| | | | | | | (65.64) | (4.16) | (9.19) | (7.00) |
| IVd | 4-$OCH_3C_6H_4$ | 4-$OCH_3C_6H_4$ | $C_{25}H_{19}N_3O_4S$ | 78% | >300* | 65.68 | 4.21 | 9.13 | 6.95 |
| | | | | | | (65.64) | (4.16) | (9.19) | (7.00) |
| Va | 4-$NH_2C_6H_4$ | - | $C_{17}H_{13}ON_5S$ | 70% | 162 | 60.93 | 3.91 | 20.83 | 9.51 |
| | | | | | | (60.89) | (3.88) | (20.89) | (9.55) |
| Vb | 4-$OCH_3C_6H_4$ | - | $C_{18}H_{14}N_4O_2S$ | 72% | 157 | 61.76 | 4.05 | 15.97 | 9.11 |
| | | | | | | (61.71) | (4.00) | (16.00) | (9.14) |
| VIa | 4-$NH_2C_6H_4$ | - | $C_{17}H_{12}N_4OS_2$ | 74% | 172 | 57.99 | 4.45 | 15.90 | 18.13 |
| | | | | | | (57.95) | (4.41) | (15.91) | (18.18) |

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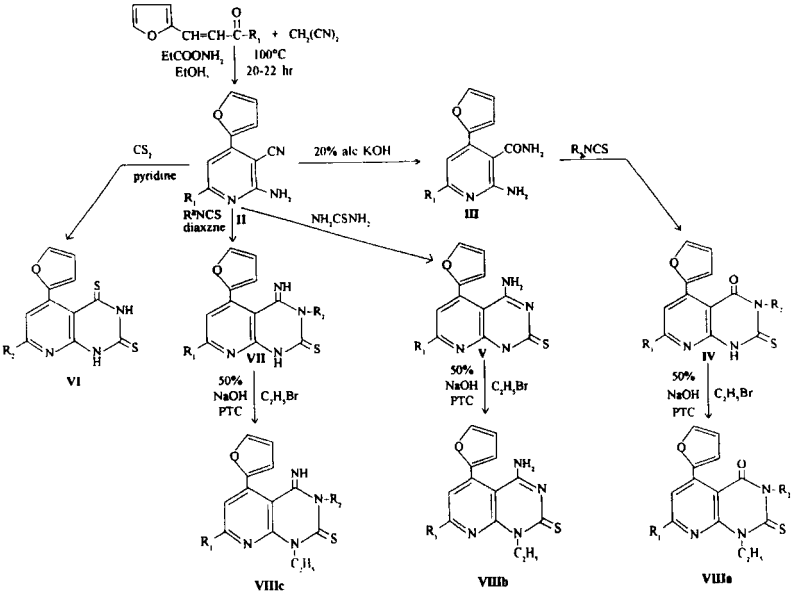
| *Compd. No.* | $R_1$ | $R_2$ | *Molecular Fourmula* | *Yield %* | *M.P. °C* | *Elemental Analysis % Found (Calcd.)* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *C* | *H* | *N* | *S* |
| VIb | 4-$OCH_3C_6H_4$ | - | $C_{18}H_{13}N_3O_2S_2$ | 78% | 274 | 58.89 | 3.57 | 11.41 | 17.40 |
| | | | | | | (58.85) | (3.54) | (11.44) | (17.44) |
| VIIa | 4-$NH_2C_6H_4$ | 2-$OCH_3C_6H_4$ | $C_{24}H_{19}N_5O_2S$ | 69% | 214 | 65.35 | 4.33 | 15.83 | 7.23 |
| | | | | | | (65.31) | (4.30) | (15.87) | (7.26) |
| VIIb | 4-$OCH_3C_6H_4$ | 4-$OCH_3C_6H_4$ | $C_{25}H_{20}N_4O_3S$ | 72% | 158 | 65.83 | 4.42 | 12.25 | 7.00 |
| | | | | | | (65.79) | (4.38) | (12.28) | (7.02) |
| $VIII_a$ | 4-$OCH_3C_6H_4$ | 4-$OCH_3C_6H_4$ | $C_{25}H_{19}O_4N_3S$ | 70% | 195 | 66.84 | 7.79 | 8.63 | 6.53 |
| | | | | | | (66.80) | (7.74) | (8.66) | (6.60) |
| $VIII_b$ | 4-$OCH_3C_6H_4$ | - | $C_{20}H_{18}N_4O_2S$ | 69% | 148 | 63.53 | 4.79 | 14.87 | 8.84 |
| | | | | | | (63.49) | (4.76) | (14.81) | (8.86) |
| $VIII_c$ | 4-$OCFH_3C_6H_4$ | 4-$OCH_3C_6H_4$ | $C_{27}H_{24}N_4O_3S$ | 72% | 169 | 66.97 | 4.99 | 11.52 | 6.57 |
| | | | | | | (66.94) | (4.96) | (11.57) | (6.61) |

* Decomposed.

The streaching vibrations of the -$NH_2$ 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 $CONH_2$.

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 $cm^{-1}$, -$NH_2$ at 3410–3300 $cm^{-1}$and >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, -$NH_2$ and >C=NH and the presence of the bands for >C=S & -NHCS confirm the structure of **VI.**




SCHEME 1

## $^1$H NMR spectra

In the $^1H$ NMR spectra -$OCH_3$ 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 $-NH_2$ 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 μg 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.

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## 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 $^1H$ 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.

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TABLE II Antimicrobial activity of synthesized compounds, zone of growth inihibition (mm) (activity index)*

| | *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) |
| IVb | 4.9 | 10.6 | 11.2 | 11.0 | 15.0 | 9.1 |
| | (0.61) | (1.18) | (1.12) | (1.1) | (1.25) | (0.76) |
| IVc | 6.0 | 5.0 | 8.9 | 9.0 | 10.5 | 7.5 |
| | (0.75) | (0.58) | (0.89) | (0.90) | (0.88) | (0.63) |
| IVd | 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 | 9.0 | 10.5 | 11.9 | 13.0 | 10.0 |
| | (0.90) | (1.00) | (1.05) | (1.19) | (1.08) | (0.84) |
| Vb | 5.2 | 8.0 | 9.8 | 10.8 | 12.0 | 12.0 |
| | (0.65) | (0.89) | (0.98) | (1.08) | (1.00) | (1.01) |
| 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) |
| VIb | 5.4 | 8.3 | 10.7 | 12.7 | 10.9 | 10.9 |
| | (0.67) | (0.92) | (1.07) | (1.27) | (0.91) | (0.91) |
| VIIa | 9.6 | 9.00 | 6.2 | 9.0 | 6.00 | 13.8 |
| | (1.20) | (1.00) | (0.62) | (0.90) | (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 | 9.0 |
| | (0.81) | (0.87) | (0.59) | (0.59) | (0.83) | (0.75) |
| VIIIc | 8.0 | 8.0 | 10.1 | 5.7 | 10.0 | 11.9 |
| | (1.00) | (0.89) | (1.01) | (0.57) | (0.83) | (1.00) |

* Activity index = Inhibition area of the sample/Inhibition area of the standard.

**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.

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**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°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 recrystallized 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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