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# NOVEL PYRIMIDINES, ISOXAZOLS AND PYRAZOLES – THEIR SYNTHESIS, CHARACTERIZATION AND MICROBIAL EVALUATION

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**Abstract:**
The chalcones were prepared by reaction of 3-acetyl pyridine and aromatic aldehydes in presence of 40% potassium hydroxide. The resultant chalcones were further converted into respective Pyrimidines, Isoxazoles and Pyrazoles by treatment with Urea or Thiourea, Hydroxylamine hydrochloride and Hydrazine hydrates. The structures of the compounds were established on the basis of spectral techniques also their antimicrobial activity was evaluated against gram positive as well as gram negative bacteria's.

**Keywords: Chalcones, Pyrimidines, Isoxazole and Pyrazoles.**

## Introduction

Chalcones are products of condensation of simple or substituted aromatic with simple or substituted acetophenones in presence of alkali. Chalcone constitute an impartment group of natural products and some of them possess a wide range of biological activities such as antimicrobial [I], anticancer[II], antitubercular [III] and antiviral [IV] etc. Chalcones and the corresponding heterocyclic analogs are valuable intermediates in organic synthesis [V] and exhibit a multitude of biological activities [VI]. From a chemical point of view, an important feature of chalcones and their heteroanalogs is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts [VII, VIII]. This type of reaction may be exploited with the view of obtaining highly functionalized cyclohexene derivatives [IX], but is more commonly used for the preparation of 3,5-diaryl-6-carbethoxycyclohexenones *via* Michael addition of ethyl acetoacetate. The mentioned cyclohexenones are efficient synthons in building spiranic compounds[X] or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles and benzothiadiazoles,[XI] benzopyrazoles and benzisoxazoles[XII-XIII] or carbazole derivatives[XIV].
In this work we have synthesized and characterized some of new heterocyclic Derivatives like pyrazole, isoxazole and pyrimidine from the chalcones and also studied its microbial activity against gram positive and gram negative bacteria's.

## Result and Discussion:

The chalcones **(3)** were prepared by reaction of 3-acetyl pyridine **(1)** and aromatic aldehydes **(2)** in presence of 40% potassium hydroxide. The resultant chalcone was further converted into

Pyrimidines **(4-5)**, Isoxazoles **(6)** and Pyrazoles **(7)** by treatment with Urea or Thiourea, Hydroxylamine hydrochloride and Hydrazine hydrates respectively. The structure of the compounds was established on the basis of spectral techniques also their antimicrobial activity was evaluated against gram positive as well as gram negative bacteria's.

**4-(4-Methoxy-phenyl)-6-pyridin-3-yl-pyrimidin-2-ol (4a).**
Yield: 87 %, 240-43°C; IR (KBr) $cm^{-1}$: 3290 (OH); 2215 (C=N), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 3.73 (s, 3H, $OCH_3$), 4.59 (s, 1H, OH), 6.88-8.21 (m, 9H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 56.3 ($OCH_3$), 120.6-130.8 (C=C & Ar-C), 168.81 (C=N), 171.54 (C=N), 174.89 (C=N). Anal. % $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.14; H, 4.61; N, 14.93.

**4-(4-Hydroxy-phenyl)-6-pyridin-3-yl-pyrimidin-2-ol (4b).**
Yield: 64 %, 216-18°C; IR (KBr) $cm^{-1}$: 3310 (OH); 2201 (C=N), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 4.87 (s, 1H, OH), 6.15 (s, 1H, OH), 6.21-8.04 (m, 9H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 122.41-131.21 (C=C & Ar-C), 169.21 (C=N), 171.89 (C=N), 176.15 (C=N). Anal. % $C_{15}H_{11}N_3O$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.74; H, 4.11; N, 15.73.

**4-(4-Methoxy-phenyl)-6-pyridin-3-yl-pyrimidin-2-thiol (5a).**
Yield: 87 %, 264-66°C; IR (KBr) $cm^{-1}$: 2250 (SH); 2215 (C=N), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 2.42 (s, 1H, SH), 3.68 (s, 3H, $OCH_3$), 6.94-8.42 (m, 9H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 56.21 ($OCH_3$), 124.12-133.24 (C=C & Ar-C), 167.9 (C=N), 172.48 (C=N), 175.64 (C=N). Anal. % $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.98; H, 4.41; N, 14.17.

**4-(4-Hydroxy-phenyl)-6-pyridin-3-yl-pyrimidin-2-thiol (5b).**
Yield: 68 %, 238-40°C; IR (KBr) $cm^{-1}$: 3290 (OH); 2251 (SH), 2190 (CN), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 3.12 (s, 1H, SH), 5.25 (s, 1H, OH), 7.42-8.32 (m, 9H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 124.48-133.14 (C=C & Ar-C), 168.98 (C=N), 172.09 (C=N), 176.30 (C=N). Anal. % $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 63.94; H, 3.91; N, 14.83.

**3-[5-(4-methoxy-phenyl)-4, 5-dihydro-isoxazol-3-yl]-pyridine (6a)**
Yield: 58 %, 246-48°C; IR (KBr) $cm^{-1}$: 2215 (C=N), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 1.8 (d, 2H, $CH_2$), 3.67 (s, 3H, $OCH_3$), 4.89 (t, 1H, CH), 7.14 -8.08 (m, 8H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 30.65 ($CH_2$), 56.21 ($OCH_3$), 69.81 (CH), 119.84-129.58 (C=C & Ar-C), 163.39 (C=N), 167.21 (C=N), Anal. % $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.78; H, 5.51; N, 11.17.

**3-[5-(4-hydroxy-phenyl)-4, 5-dihydro-isoxazol-3-yl]-pyridine (6b).**
Yield: 61 %, 221-23°C; IR (KBr) $cm^{-1}$: 3315 (OH); 2205 (CN), $^{1}H$ NMR (DMSO-$d_6$, δ , ppm): 1.78 (d, 2H, $CH_2$), , 4.74 (t, 1H, CH), 5.14 (s, 1H, OH), 7.28 -8.35 (m, 8H, Ar-H); $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 30.52 (CH2), 56.13 ($OCH_3$), 69.48 (CH), 121.01-130.42 (C=C & Ar-C), 164.15 (C=N), 166.92 (C=N), Anal. % $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 4.98; N, 11.57.

**3-[5-(4-methoxy-phenyl)-4, 5-dihydro-1*H*-pyrazol -3-yl]-pyridine (7a)**
Yield: 68 %, 258-60°C; IR (KBr) $cm^{-1}$: 3310 (NH), 2204 (C=N), $^1H$ NMR (DMSO-$d_6$, δ , ppm): 1.94 (d, 2H, $CH_2$), 3.75 (s, 3H, $OCH_3$), 4.21 (t, 1H, CH), 7.25 -8.32 (m, 8H, Ar-H), 8.54 (s, 1H, NH), $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 29.98 (CH2), 56.74 ($OCH_3$), 71.24 (CH), 121.54-130.62 (C=C & Ar-C), 164.24 (C=N), 166.88 (C=N), Anal. % $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.08; H, 5.91; N, 16.47.

**3-[5-(4-hydroxy-phenyl)-4, 5-dihydro-1*H*-pyrazol -3-yl]-pyridine (7b)**
Yield: 69 %, 245-47°C; IR (KBr) $cm^{-1}$: 3324 (OH); 2225 (CN), $^1H$ NMR (DMSO-$d_6$, δ , ppm): 1.84 (d, 2H, $CH_2$), , 4.32 (t, 1H, CH), 5.41 (s, 1H, OH), 7.34 -8.14(m, 8H, Ar-H), 8.65 (s, 1H, NH), $^{13}C$ NMR (DMSO-$d_6$, δ , ppm): 30.14 (CH2), 56.45 ($OCH_3$), 70.95 (CH), 120.87-129.51 (C=C & Ar-C), 163.64 (C=N), 166.25 (C=N), Anal. % $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.21; H, 5.39; N, 17.45.

**Experimental**
Melting points were determined on a capillary melting point apparatus and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in the indicated solvent on Joul 300 MHz spectrophotometer using TMS as an internal standard. Infrared spectra were recorded in Bruker FTIR spectrophotometer. Microanalyses were performed on Carlo Ebra 1108 element analyzer and were within the ± 0.5% of the theoretical values. Column chromatography was performed on silica gel (Merck, 100-200 mesh).

**Synthesis of Chalcones (3)**
An ethanolic solution of 3-acetylpyridine **(1)** (0.01mol) and substituted aromatic aldehydes **(2)** (0.01 mol) in presence of catalytic amount of 40% KOH was stirred for 6 hrs at room temperature. The progress of the reaction was monitored on TLC. Upon Completion, the mixture was poured onto crushed ice. The separated product was filtered, washed with water and recrystallized from ethanol.

**Synthesis of 4-(4-substituted-phenyl)-6-pyridin-3-yl-pyrimidin-2-ol (4)**
A mixture of Chalcone **(3)** (0.02mol), Urea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was reflux for 6-8 hrs. The progress of the reaction was monitored on TLC. Upon Completion, the concentrated mixture was poured onto crushed ice. The separated product was filtered, washed with water and recrystallized from ethanol.

**Synthesis of 4-(4-Hydroxy-phenyl)-6-pyridin-3-yl-pyrimidin-2-thiol (5)**
A mixture of Chalcone **(3)** (0.02mol), Thiourea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was refluxed for 6-8 hrs. The progress of the reaction was monitored on TLC. Upon Completion, the concentrated mixture was poured onto crushed ice. The separated product was filtered, washed with water and recrystallized from ethanol.

**Synthesis of 3-[5-(4-substituted-phenyl)-4, 5-dihydro-isoxazol-3-yl]-pyridine (6)**
A mixture of Chalcone **(3)** (0.02mol), hydroxylamine hydrochloride (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was refluxed for 6-8 hrs. The progress of the reaction was monitored on TLC. Upon Completion, the concentrated mixture was poured onto crushed ice. The separated product was filtered, washed with water and recrystallized from ethanol.

**Synthesis of 3-[5-(4-hydroxy-phenyl)-4, 5-dihydro-1*H*-pyrazol -3-yl]-pyridine (7)**
A mixture of Chalcone **(3)** (0.02 mol), hydrazine hydrate (0.02 mol) and glacial acetic acid (10 ml) in ethanol (25 ml) was refluxed for 6-8 hrs. The progress of the reaction was monitored on TLC. Upon Completion, the mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from ethanol.

**Antimicrobial and antifungal activities**
All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in following **Table 1**.

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**Scheme I**

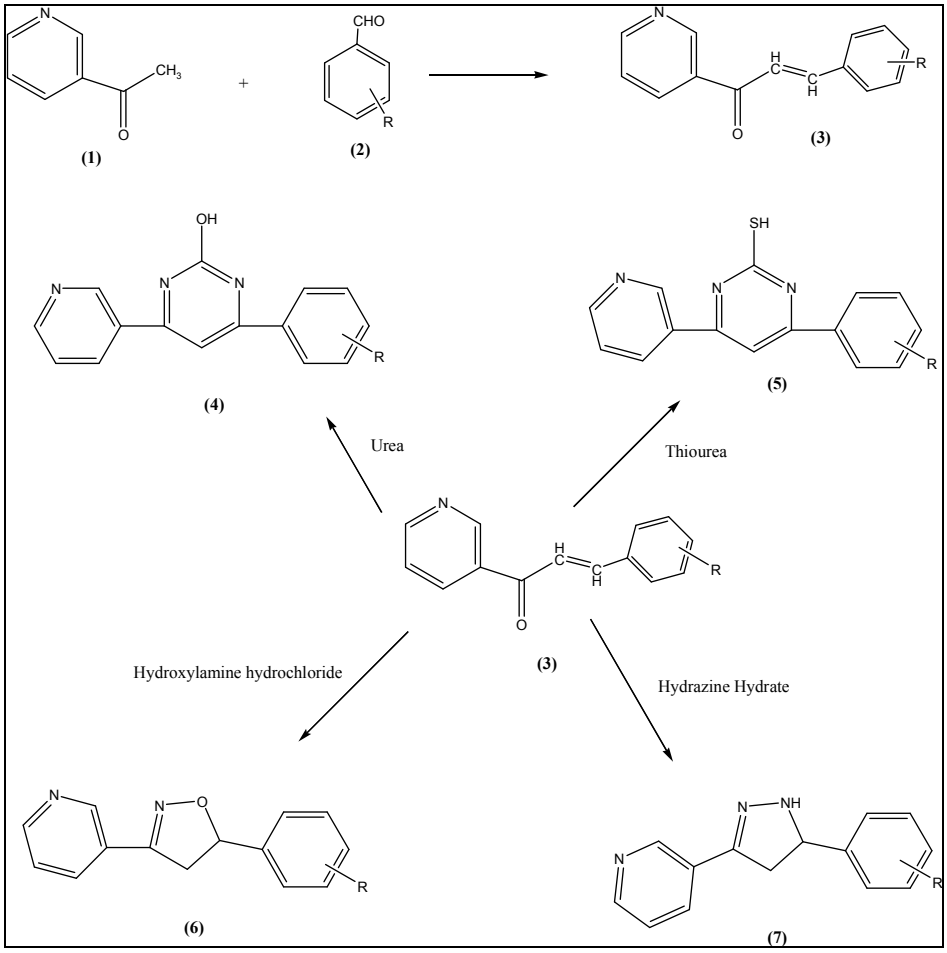

**Table 1: Antimicrobial Evaluation of Synthesized compounds (4-7)**

| Compds | Zone of inhibition (in mm)* | | | |
|---|---|---|---|---|
| | Gram Positive | | Gram Negative | |
| | *S.aureus* | *C. diphtheria* | *E. coli* | *P. aeruginosa* |
| **4a** | 17 | 18 | 17 | 17 |
| **4b** | 24 | 23 | 18 | 16 |
| **5a** | 21 | 20 | 20 | 20 |
| **5b** | 18 | 18 | 15 | 17 |
| **6a** | 23 | 20 | 17 | 15 |
| **6b** | 20 | 22 | 20 | 18 |
| **7a** | 23 | 21 | 18 | 17 |
| **7b** | 18 | 17 | 15 | 16 |
| **10c** | 24 | 23 | 21 | 20 |
| **10e** | 22 | 20 | 18 | 18 |
| **Ciprofloxacin** | 25 | 24 | 24 | 22 |
| **DMSO** | 0 | 0 | 0 | 0 |

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