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Synthesis, Characterization And Biological Screening Of 3-(2-Amino Pyrimidin-4-Yl) Quinoxalin-2-Ol Derivatives

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Abstract: Synthesis of some 2-aminopyrimidine [1a-e] have been synthesized by the condensation of quinoxaline based chalcone with guanidine hydrochloride in ethanol. The structural assignment of the compounds was based on elemental analysis, IR, ^{1}H NMR data and mass analysis. All the synthesized compounds have been screened for their antibacterial activity.

Keywords: 2-aminopyrimidine, Quinoxaline, Chalcone.

1. INTRODUCTION:

A large number of heterocycles compounds derived from chalcone group have been reported as active biological entities, where 2-aminopyrimidine play a vital role owing to their wide range of therapeutic activities. Thus significant biological properties associated with pyrimidine derivatives have aroused considerable interest to design the compound with better drug potential and to study their pharmacological profile. Generally pyrimidine derivatives such as 2-hydroxy pyrimidine, 2-mercapto pyrimidine and 2-aminopyrimidine are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates. The first primary synthesis from aliphatic fragments was carried out by Frankland and co-workers in 1848, since then a many distinct primary synthetic method have been devised [1-2]. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrole[3] , imidazole[4] , isoxazoles and oxazoles[5-6], pyridines[7] , pyrazines[8] , 1,3,5-triazines[9] , oxazines[10], thiazines[11] by variety of processes. 2- Aminopyrimidines exhibit a wide spectrum of pharmacological activities like, antimicrobial[12-17], antitumor[18], cardiovascular[19], inflammatory[20] and antiviral[21]. Derivatives of Quinoxaline are widely used as bridging ligand in both homobimetallic and heterobimetallic complexes. They have wide variety of biological applications including in optoelectronic devices self extinguishing and flame resistance polymer, flourophores photo

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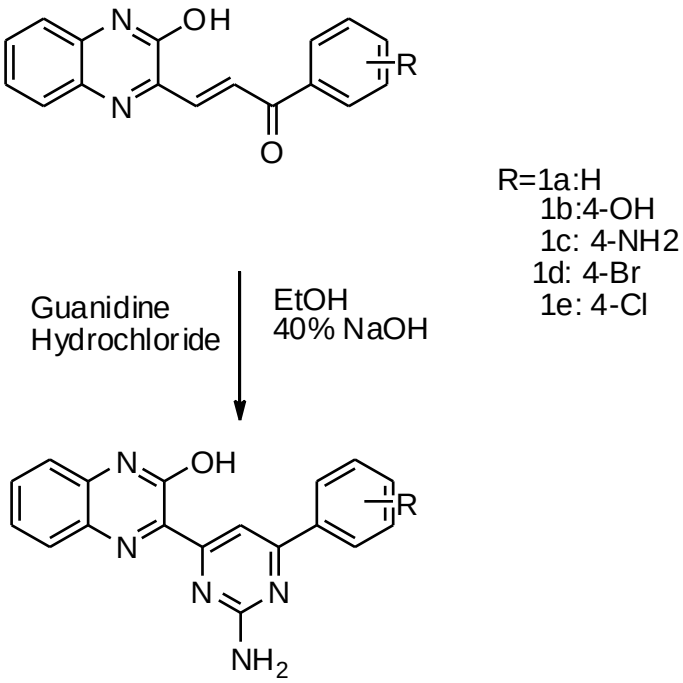
sensitizers, corrosion inhibitor and electron transport material. In present work we have synthesized 3-(2-amino pyrimidin-4-yl) quinoxalin-2-ol derivatives by condensing quinoxaline based chalcone with guanidine hydrochloride in ethanol (**Scheme-1**).



3-(2-amino-6-phenylpyrimidin-4-yl)quinoxalin-2-ol derivatives

Scheme1: synthesis of 3-(2-amino-6-phenylpyrimidin-4-yl)quinoxalin-2-ol derivatives

2. MATERIALS AND METHODS:

2.1 Materials and Physical Measurements

All chemicals used were of high purity analytical grade. Organic solvents like absolute ethyl alcohol supplied by Loba. Substituted acetophenones supplied by Sigma Aldrich. 3-Hydroxyquinoxaline-2-carboxaldehyde was prepared as previously described [22]. Thin layer chromatography was carried out on silica gel 60/UV254. Melting points of products were recorded in open capillaries on digital melting point apparatus (Optics Technology) and were uncorrected. IR spectra of ligand were recorded on Perkin-Elmer FTIR Spectrophotometer in range 4000-650 cm-1 using ATR Instrument. IR spectra of metal complexes were recorded in

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KBr at 4000-400 cm-1 at SAIF Kochi. 1H NMR spectra were obtained on a Perkin-Elmer 300 MHz spectrophotometer using TMS as internal standard in CDCl3 as solvent at SAIF Kochi. Elemental analyses were performed on elementar vario EL-III at SAIF Kochi.Biological activities at department of Biotechnology Aditya College, Beed.

Preparation of 3-(2-amino-6-phenylpyrimidin-4-yl)quinoxalin-2-ol derivatives:

Entitled compound was prepared at reflux temperature by condensation reaction of prepared chalcone (0.01mole), in 250ml round bottom flask with guanidine hydrochloride by using alcohol as solvent and 40% NaOH solution was added to make pH basic**.** The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, neutralized with dilute hydrochloric acid and the mixture was agitated for 5 to 10 minutes. The product was separated by filtration and recrystallized from ethanol. Synthetic pathway for preparation of title compounds is shown in reaction **Scheme-1**.

Table-1: Physical data of (1a-1e)

Sr. no.	Colour	Mol. formula	Mol. Weight	Elemental Analysis found %			
				C	H	N	X
1a	Yellow	$C_{18}H_{13}N_5O$	315.33	68.56	4.16	22.21	--
1b	Dark yellow	$C_{18}H_{13}N_5O_2$	331.33	65.25	3.95	21.14	--
1c	Brick red	$C_{18}H_{14}N_6O$	330.34	65.44	4.27	25.44	--
1d	yellow	$C_{18}H_{12}BrN_5O$	394.22	54.84	3.07	17.76	20.27
1e	Yellowish green	$C_{18}H_{12}ClN_5O$	349.77	61.81	3.46	20.02	10.14

2.2 Spectroscopic data of synthesized derivatives (1a-1e)

1a. 3-(2-amino-6-phenylpyrimidin-4-yl) quinoxalin-2-ol(1a)

% Yield: 60. MP (°C): 167. IR (KBr, cm^{-1}): 3128, 3371, 1543, 1053.^{1}H NMR (DMSO, 400 MHz) δ:11.50(1H,s,Ar–OH), 7.40-7.90(10H, m, Ar–H), 6.70(2H, s, -NH2). mass(m/z):315.

1b. 3-(2-amino-6-(4-hydroxyphenyl)pyrimidin-4-yl)quinoxalin-2-ol(1b)

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% Yield: 65. MP (°C): 145. IR (KBr, cm^{-1}): 3138, 3371,1620, 1543, 1053. ^{1}H NMR (DMSO, 400 MHz) δ:11.53(1H,s,Ar–OH), 7.50-7.90(7H, m, Ar–H), 6.90(2H, s, -NH2). 6.80(2H, d, Ar-H). 5.30(1H, s, Ar-OH). mass(m/z):331.

1c. 3-(2-amino-6-(4-aminophenyl)pyrimidin-4-yl)quinoxalin-2-ol(1c)

% Yield: 70. MP (°C): 170. IR (KBr, cm^{-1}): 3138, 3300, 3350,1620, 1543, 1053. ^{1}H NMR (DMSO, 400 MHz) δ:11.53(1H,s,Ar–OH), 7.50-7.90(7H, m, Ar–H), 7.00(2H, s, -NH2). 6.80(2H, d, Ar-H). 6.20(2H, s, Ar-NH2). mass(m/z):330.

1d. 3-(2-amino-6-(4-bromophenyl)pyrimidin-4-yl)quinoxalin-2-ol(1d)

% Yield: 80. MP (°C): 165. IR (KBr, cm^{-1}): 3128, 3371, 1543, 1053. ^{1}H NMR (DMSO, 400 MHz) δ:11.50(1H,s,Ar–OH), 7.40-7.90(9H, m, Ar–H), 6.70(2H, s, -NH2). mass(m/z):394.

1e. 3-(2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)quinoxalin-2-ol(1e)

% Yield: 67. MP (°C): 150. IR (KBr, cm^{-1}): 3128, 3371, 1543, 1053, 1035 ^{1}H NMR (DMSO, 400 MHz) δ: 11.50(1H,s,Ar–OH), 7.40-7.80(9H, m, Ar–H), 6.75(2H, s, -NH2). mass(m/z):315.

2.3 Antimicrobial Activity

All the synthesised compounds were evaluated for their antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441) by using ampicillin, chloramphenicol and ciprofloxacin as the standard antibacterial drugs. The antibacterial screening of compound **[1a-1e]** pointed out that in Gram-positive bacteria, compounds **1b** (MIC=100 µg/ml) showed an outstanding inhibitory effect against *Staphylococcus aureus* as compared to ampicillin (MIC=250 µg/ml) and admirable to chloramphenicol and ciprofloxacin (MIC=50 µg/ml). Compounds **1c** showed equipotential activity to ampicillin (MIC=250 µg/ml) while compounds **1a**, **1d** found to possess comparable activity to ampicillin (MIC=250 µg/ml) and modest to chloramphenicol and ciprofloxacin (MIC=50 µg/ml) against *Staphylococcus aureus* organism. In case of inhibiting *Streptococcus pyogenes*, compounds **1c** (MIC=100 µg/ml) exhibited inhibitory effect as same as ampicillin (MIC=100 µg/ml) and less effective than chloramphenicol and ciprofloxacin (MIC=50 µg/ml) whereas compounds **1b**, **1e** (MIC=125 µg/ml)exerted significant potential to ampicillin

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(MIC=100 µg/ml) and less potential to chloramphenicol and ciprofloxacin (MIC=50 µg/ml) against *Streptococcus pyogenes*.

In case of inhibiting Gram-negative bacteria, compounds **1d** (MIC=62.5 µg/ml)demonstrated excellent activity compared to ampicillin (MIC=100 µg/ml) while compounds**1b**(MIC=100 µg/ml) showed equipotential to ampicillin (MIC=100 µg/ml) and less potential to chloramphenicol (MIC=50 µg/ml) and ciprofloxacin (MIC=25 µg/ml) against *Escherichia coli*.

The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and were found less effective than the employed standard drugs. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-negative bacteria rather than Gram-positive bacteria.

Table-2: In vitro antimicrobial activity of the synthesized compounds [1a-1e]

Antimicrobial activity(MIC) µg/ml				
Entry	**Antibacterial activity**			
	Gram positive Bacteria		**Gram negative Bacteria**	
	S.*aureus*	**S.*pyogenes***	**E.*coli***	**P.*aerug***
1a	500	200	250	250
1b	100	100	100	200
1c	100	100	125	125
1d	250	250	62.5	250
1e	500	125	250	125
Ampiciliin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25

3. RESULTS AND DISCUSSION:

As an example, in the IR spectrum of compound 3a, characteristic is the C=N stretching vibration, which appear as an intense band at 1543 cm^{-1} in all compounds. Band at 3371 cm^{-1} observed due to NH_2 group in compounds. The FTIR spectra of the compounds was also exhibited bands corresponding to the structural characteristic for the (3a); the stretching vibration band for the -C=N functionality, C=C linkage and C-O stretching observed at 1543, 1620 and 1053cm^{-1} respectively. Several medium intensity bands appeared at 1540 and 3040 cm^{-1} region of the spectra were due to the stretching of C=C and =C-H vibrations of aromatic ring. The ^{1}H

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NMR spectrums of compound 3a aromatic protons for the substituted benzene ring were found again in the range at δ 7.40-7.90 ppm as multiplet signal. 1H NMRspectra 1a showed the peak at δ 6.70 ppm (s, 2H, NH_2) in all compounds peak at δ 11.50-11.55 ppm (s, 1H, Ar-OH) observed.

4. CONCLUISION:

Our present study is focused on the reactions, synthesis, spectral analysis and Microbial activities of 3-(2-amino-6-phenylpyrimidin-4-yl) quinoxalin-2-ol derivatives. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-negative bacteria rather than Gram-positive bacteria.

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