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Synthesis and Antibacterial Activity of 2-(4,5-Dihydro-3-substituted-1*H*-pyrazol-5-yl)-3-methoxyquinoxalines

T. Rajani Devi[1,2], E. Laxminarayana[3], T. Giri[3], M. Thirumala Chary[1]*

[1]Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India
[2]Department of Chemistry, Christu Jyoti Institute of Technology and Science, Jangaon, Telangana, India
[3]Department of Chemistry, Sreenidhi Institute of Science and Technology (Autonomous), Hyderabad, Telangana, India

ABSTRACT A new series of 2-(4,5-dihydro-3-substituted-1*H*-pyrazol-5-yl)-3-methoxyquinoxalines **(5a-e)** was synthesized by the cyclocondensation of 3-(2-hydroxyquinoxalin-3-yl)-1-phenylprop-2-en-1-ones **(4a-e)** with hydrazine hydrate. The compounds **4a-e** were prepared through a three-step procedure starting from ethyl 3-methoxy-quinoxaline-2-carboxylate (1). All the compounds **4a-e** and **5a-e** were thoroughly characterized by spectral and elemental analysis. The newly synthesized quinoxalines **5a-e** were tested for their antibacterial activity.

KEYWORDS Quinoxaline, Dess–Martin periodinane, Pyrazole, Antibacterial activity.

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INTRODUCTION

Quinoxaline derivatives are an important class of heterocyclic compounds, where N replaces some carbon atoms in the ring. Quinoxaline is rare in natural state, but their synthesis is easy to perform.[1] A slight modification in its structure is possible to obtain a wide variety of compounds with different broad range of biological activities and pharmacological applications[2] such as bactericidal and insecticidal,[3] antibacterial,[4-7] antifungal,[4,8] anti-protozoan,[9,10] and antitubercular activity.[11-14] Certain condensed quinoxalines exhibit antibacterial, analgesic, tuberculostatic, and antileukemic activities.[15] It also found that several highly mutagenic and carcinogenic quinoxalines have been identified in heated meat and fried fish.[16] Quinoxaline-diones derivatives are used for the treatment of epilepsy, pain, and other neurodegenerative disorders. Biologically active peptide antibiotics such as levomycin and echinomycin have been shown to possess one or more quinoxalinyl residues.

Quinoxalines have a wide range of applications in DNA cleaving agent, dyes, organic semiconductors, cavitands, efficient electroluminescent, dihydroannunulenes, and building blocks for the synthesis of anion receptor.

In addition, the pyrazole derivatives have many applications on crop protection chemistry and are used as herbicidal, fungicidal and insecticidal agents. Hence, pyrazole derivatives have attracted much attention of chemists. In continuation of earlier work[17-19] and as part of our research program, we synthesized and characterized some new pyrazolylquinoxaline derivatives.

RESULTS AND DISCUSSION

The target compounds were synthesized according to the reactions sequence outlined in **Scheme 1.** Ethyl 3-methoxy-quinoxaline-2-carboxylate (**1**) was reacted with the lithium aluminum hydride to afford alcohol **2**. When alcohol **2** was subjected to oxidation with Dess–Martin periodinane, it produced aldehyde **3**. The compound **3** on reaction with acetophenones in the presence of KOH resulted in the formation of **4a-e**. Finally, condensation of **4a-e** with hydrazine hydrate in EtOH presence of AcOH gave target compounds **5a-e**.

*Corresponding author: Email: mtcharya@yahoo.com

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ANTIBACTERIAL ACTIVITY

All the synthesized pyrazolylquinoxalines **5a-e** were screened for their antibacterial activity against *Bacillus subtilis Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae* at 100 mg/mL concentration. The compounds possessing chlorophenyl, fluorophenyl groups as substituents exhibited good activity against the tested bacteria.

The antimicrobial assay was carried out by the well diffusion method. A standardized 1–2 × 10^7 cfu/mL 0.5 McFarland standards were introduced on to the surface of the sterile agar plate and evenly distributed the inoculums using a sterile glass spreader. Simultaneously, 8 mm wells were cut from the plate using a sterile cork borer. Sixty microliters of the pigment at 100 mg/mL were introduced into each well. The agar plates were incubated aerobically at 37°C. After 24 h, the inhibition zones were measured with a ruler and compared with the control well containing only dimethyl sulfoxide (DMSO) and 10 mg/mL of Gentamicin as standard.

The results of each compound are shown in **Table 1.** Control inhibition zone (which indicates the inhibition zone of solvent) was subtracted from the inhibition zone of compounds, which gives the actual inhibition zone of compounds.

A perusal of **Table 1** reveals that the compounds **5b**, **5c,** and **5e** are more toxic than **5a** and **5d** compounds**.**

EXPERMENTAL SECTION

All the chemicals and reagents were purchased from Aldrich. All the solvents used were of high-performance liquid chromatography grade. Thin-layer chromatography (TLC) was checked by Merck AL silica gel 60 F_{254} plates and visualized under ultraviolet light. Melting points were recorded on a Buchi melting point M-565 instrument. ^{1}H NMR spectra were recorded in DMSO-d_6 with a Varian Mercury Plus 400 MHz instrument. All the chemical shifts were reported in δ (ppm) using tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LCMS-QP 1000 mass spectrometer. All the reactions were performed under an inert atmosphere.

3-Methoxyquinoxaline-2-carbaldehyde (3)

To a stirred solution of, (2-methoxyquinoxalin-3-yl) methanol (**2**) (5 g, 26.31 mmol) in DCM (100 mL) was added Dess–Martin periodinane (22.3 g, 52.63 mmol) and the reaction was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice-cold water and extracted from 40% EtOAc in pet. ether to afford 3-methoxyquinoxaline-2-carbaldehyde (**3**) as off white solid, 78%, m.p.146–148°C.

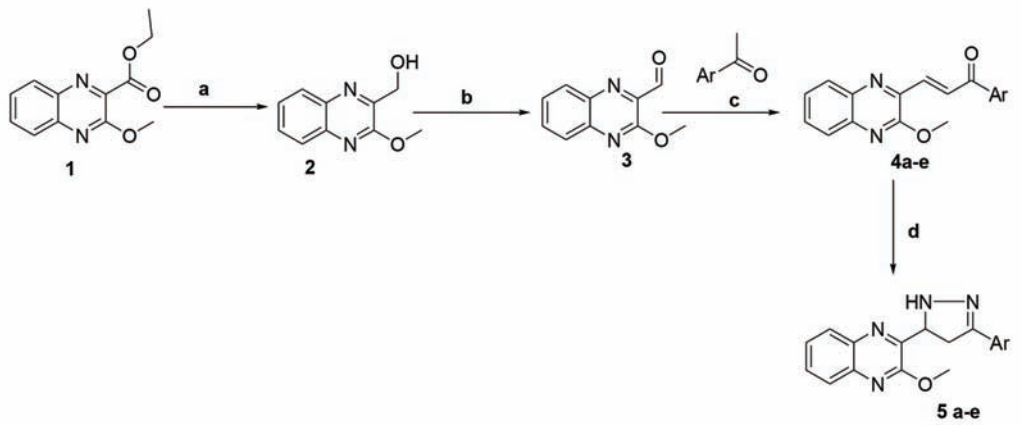
^{1}H NMR (DMSO-d_6), 400 MHz: δ =9.97 (s, 1H), 8.11 (d, 2H, *J* = 7.8 Hz), 7.92 (t, 2H, *J* = 2.8 Hz), 3.78 (s, 3H); Mass =188.9 $[M+H]^+$.

3-(2-Methoxyquinoxalin-3-yl)-1-phenylprop-2-en-1-one (4)

To a stirred solution, 3-methoxyquinoxaline-2-carbaldehyde (**3**) (4g, 21.27 mmol) in EtOH (40 mL) was added acetophenone (3 g, 25.53 mmol) and KOH powder (1.4 g, 25.53 mmol) and the mixture was stirred at 90°C for 18 h. After completion of the reaction, the reaction mixture was poured into ice-cold water, extracted with EtOAc. Combined extracts were washed with water, brine

Table 1: Antibacterial activities of 5a-e

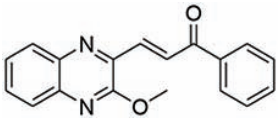
Bacteria	5a	5b	5c	5d	5e	Gentamycin
Gram-positive						
Bacillus subtilis	4	2	5	4	8	19
Bacillus cereus	6	7	3	2	12	14
Staphylococcus aureus	3	5	8	5	7	16
Gram-negative						
Escherichia coli	7	2	7	5	8	13
Proteus vulgaris	5	1	4	3	12	20
Klebsiella pneumoniae	3	4	6	4	9	15



Reagents and conditions: **a.** LAH, THF, 0°C-RT, 2 h; **b.** DCM, Dess–Martin periodinane, RT, 4h; **c.** EtOH, KOH, 90°C, 18 h; **d.** N2H4, EtOH, AcOH, 90°C, 18 h;

Scheme 1: Synthesis of 2-(4,5-dihydro-3-substituted-1*H*-pyrazol-5-yl)-3-methoxyquinoxalines (5a-e). Ar= phenyl(4a,5a), 3-chlorophenyl (4b,5b), 4-chlorophenyl(4c,5c), 4-hydroxyphenyl(4d,4d), 4-methoxyphenyl(4e,5e)

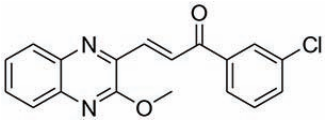
solution, dried over anhy. Na_2SO_4, and distilled to remove the solvent. The crude solid product was purified by column chromatography; the required product was eluted with 60% EtOAc in pet. ether to afford 3-(2-methoxyquinoxalin-3-yl)-1-phenylprop-2-en-1-one as off white solid, 83%; the other derivatives were also prepared following the same procedure.



3-(2-methoxyquinoxalin-3-yl)-1-phenylprop-2-en-1-one (4a)

^{1}H NMR (DMSO-d_6), 400 MHz: δ =8.21 (d, 2H, *J* = 8.2 Hz), 8.13 (d, 1H, *J* = 7.8 Hz), 7.92 (t, 2H), 7.78 (d, 2H, *J* = 8.2 Hz), 7.40–7.62 (m, 4H), 3.84 (s, 3H); Mass =290.9 $[M+H]^+$, m. p. 232–234°C

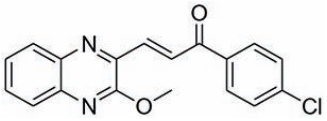
Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.45; H, 4.84; N, 9.52, found: C, 73.14; H, 3.98; N, 8.74.



1-(3-chlorophenyl)-3-(2-methoxyquinoxalin-3-yl)prop-2-en-1-one (4b)

^{1}H NMR (DMSO-d_6), 400 MHz: δ =8.19 (d, 2H, *J* = 8.0 Hz), 8.12 (t, 2H), 8.01 (d, 1H, *J* = 8.0 Hz), 7.70 (d, 2H, *J* = 8.0 Hz), 7.38–7.58 (m, 3H), 3.82 (s, 3H), Mass =325.4 $[M+H]^+$, m. p. 230–232°C

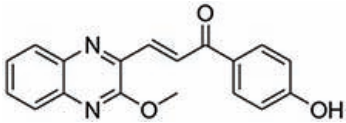
Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 65.33; H, 4.33; N, 8.22, found: C, 64.87; H, 3.54; N, 7.57.



1-(4-chlorophenyl)-3-(2-methoxyquinoxalin-3-yl)prop-2-en-1-one (4c)

^{1}H NMR (DMSO-d_6, 400 MHz): δ =8.19 (d, 2H, *J* = 8.0 Hz), 8.12 (t, 2H), 7.98 (d, 2H, *J* = 8.0 Hz), 7.71 (m, 2H), 7.42 (d, 2H, *J* = 7.8H), 3.86 (s, 3H); Mass =325 $[M+H]^+$, m. p. 235–237°C

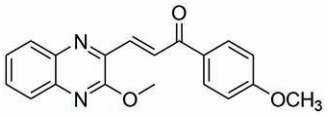
Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 65.33; H, 4.33; N, 8.22, found: C, 64.87; H, 3.54; N, 7.57.



1-(4-hydroxyphenyl)-3-(2-methoxyquinoxalin-3-yl)prop-2-en-1-one (4d)

^{1}H NMR (DMSO-d_6, 400MHz): δ = (9.61 brs, 1H), 8.13 (d, 2H, *J* = 8.2Hz), 7.98 (d, 2H, *J* = 7.80Hz), 7.78(d, 2H, *J* = 8.20), 7.7(d, 2H), 7.40 (d, 2H, *J* = 7.80Hz), 3.85(s, 3H); Mass =307 $[M+H]^+$, m.p. 272–274°C.

Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.52; H, 4.85; N, 9.05, found: C, 69.54; H, 4.42; N,8.95.



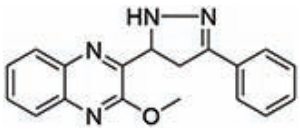
1-(4-methoxyphenyl)-3-(2-methoxyquinoxalin-3-yl)prop-2-en-1-one (4e)

^{1}H NMR (DMSO-d_6, 400MHz): δ =8.13 (d, 2H, *J* = 8.0Hz), 8.08 (m, 2H), 7.92 (d, 2H, *J* = 8.4Hz), 7.69 (d, 2H), 7.42 (m, 2H), 3.78 (s, 3H), 3.86 (s, 1H); Mass =321 $[M+H]^+$, m.p. 240–242°C.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.22; H, 5.48; N, 8.47, found: C, 70.54; H, 5.24; N, 7.88.

2-(4,5-dihydro-3-phenyl-1*H*-pyrazol-5-yl)-3-methoxyquinoxalines (5a-e)

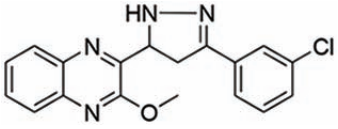
To a stirred solution, 3-(2-methoxyquinoxalin-3-yl)-1-phenylprop-2-en-1-one (**4a**) (1 g, 3.95 mmol) in EtOH (10 mL) were added hydrazine hydrate (0.252 g, 7.90 mmol) and AcOH (0.474 g, 7.90 mmol) and stirred the reaction at 90°C for 18 h. Progress of reaction was checked by TLC, after completion of reaction, the reaction mixture was poured into ice cold water and filtered the formed precipitate. Dried the precipitate under vacuum to afford 2-(4,5-dihydro-3-phenyl-1H-pyrazol-5-yl)-3-methoxyquinoxaline as off white solid, 91%, the other derivatives were also prepared following the same procedure.



2-(4,5-dihydro-3-phenyl-1H-pyrazol-5-yl)-3-methoxyquinoxaline (5a)

^{1}H NMR (DMSO-d_6, 400MHz): δ =8.12 (d, 2H, *J* = 8.0Hz), 7.90 (t, 2H), 7.78 (d, 2H, *J* = 7.8Hz), 7.61 (m, 3H), 4.41 (brs, 1H), 4.09 (m, 1H), 3.81 (s, 3H), 1.92 (m, 1H), 1.82 (m, 2H); Mass=305 $[M+H]^+$, m.p. 246–248°C.

Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.52; H, 5.24; N, 18.41, found: C, 70.41; H, 4.85; N,17.02.

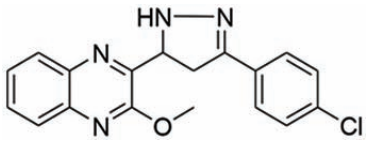


2-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-3-methoxyquinoxaline (5b)

^{1}H NMR (DMSO-d_6, 400MHz): δ =8.11(d, 2H, *J* = 8.1Hz), 7.91 (t, 2H), 7.76 (d, 2H, *J* = 8.0Hz),

7.58 (m, 2H), 4.42 (brs, 1H), 4.10 (m, 1H), 3.86 (s, 3H), 1.90 (m, 1H), 1.80 (m, 1H); Mass =339 $[M+H]^+$, m.p. 261–263°C.

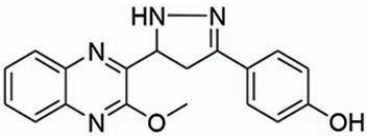
Anal. Calcd for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.21; N, 16.25, found: C, 62.55; H, 3.84; N, 15.46.



2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-3-methoxyquinoxaline (5c)

^{1}H NMR (DMSO-d_6, 400MHz): δ =8.12 (d, 2H, *J* = 8.2Hz), 7.92 (t, 2H), 7.77 (d, 2H, *J* = 8.0Hz), 7.60 (d, 2H, *J* = 8.2Hz), 4.60 (brs, 1H), 4.09 (m, 1H), 3.85 (s, 3H), 1.91 (m, 1H), 1.81 (m, 1H); Mass =339 $[M+H]^+$, m.p. 269–271°C.

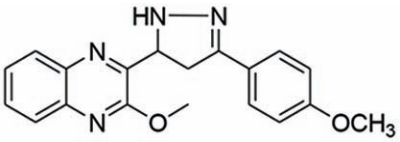
Anal. Calcd for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.21; N, 16.25, found: C, 62.55; H, 3.84; N, 15.98.



2-(3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)-3-methoxyquinoxaline (5d)

^{1}H NMR (DMSO-d_6, 400MHz): δ =10.10 (brs, 1H), 8.15 (d, 2H, *J* = 8.4Hz), 8.02 (t, 2H), 7.88 (d, 2H, *J* = 8.2Hz), 7.70 (d, 2H, *J* = 8.2Hz), 4.55 (brs, 1H), 4.08 (m, 1H), 3.84 (s, 3H), 1.89 (m, 1H), 1.79 (m, 1H); Mass =321 $[M+H]^+$ m.p. 285–287°C.

Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.46; H, 4.78; N, 17.46, found: C, 66.86; H, 4.54; N, 16.98.



2-(3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)-3-methoxyquinoxaline (5e)

^{1}H NMR (DMSO-d_6, 400MHz): δ =8.20 (d, 2H, *J* = 8.0Hz), 7.98 (t, 2H), 7.68 (d, 2H, *J* = 8.0Hz), 7.59 (d, 2H, J = 7.8Hz), 4.50 (brs, 1H), 4.08 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 1.91 (m, 1H), 1.81 (m, 1H); Mass =335 $[M+H]^+$, m.p. 264–267°C.

Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.44; N, 16.34, found: C, 67.24; H, 5.11; N, 15.88.

CONCLUSION

The present paper describes the synthesis and antibacterial activity of five new pyrazolylquinoxaline derivatives. All the compounds were obtained in good yield and compounds **5b**, **5c**, and **5e** are more toxic toward all bacteria.

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