

A new facile and efficient synthesis of 2-((5-aryl-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline and 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate derivatives

Shashikala Kethireddy ¹, Hemalatha Kotakommula ²,
Laxminarayana Eppakayala ³ and Thirumala Chary Mariganti ^{2,*}

¹Geethanjali College of Engineering and Technology, Keesara, Rangareddy, 501301, Telangana, India

²Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India

³Sreenidhi Institute of Science and Technology, Ghatkesar, Hyderabad, 501301, Telangana, India

* Corresponding author at: Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India.
Tel.: +91.984.8511562. Fax: +91.984.8511562. E-mail address: mtcharya@yahoo.com (T.C. Mariganti).

ARTICLE INFORMATION



DOI: 10.5155/eurjchem.8.2.125-129.1553

Received: 11 February 2017

Received in revised form: 19 March 2017

Accepted: 19 March 2017

Published online: 30 June 2017

Printed: 30 June 2017

KEYWORDS

Tetrazole
Quinoxalines
Antiviral activity
1,3,4-Oxadiazole
Antibacterial activity
Anticonvulsant activity

ABSTRACT

Newly synthesized compounds containing quinoxaline ring fused with tetrazoles and oxadiazoles show array of pharmacological activities, especially, anti-inflammatory, analgesic and anticonvulsant activities. The ability to serve as surrogates or bioisosteres for carboxylic acids, esters and carboxamides made them important moieties in drug designing. Considering the importance of quinoxalines, tetrazoles and 1,3,4-oxadiazoles to both medicinal and heterocyclic chemistry, the following 2-((5-aryl-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline and 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate derivatives are synthesized. The structures of the synthesized compounds were confirmed by ¹H NMR, ¹³C NMR and Mass spectral data. All the synthesized derivatives were tested *in vitro* for their antibacterial activity.

Cite this: *Eur. J. Chem.* 2017, 8(2), 125-129

1. Introduction

Tetrazoles are heterocyclic, five-membered rings containing four nitrogens and one carbon atom (CN₄H₂) [1]. Presence of four nitrogen atoms makes them acidic. They undergo electrophilic as well as nucleophilic substitution [2]. They can act as pharmacophore for the carboxylate group, which increases their utility. Tetrazoles are Angiotensin II blockers as in Losartan and Candesartan [1,3,4]. Tetrazoles and its derivatives show most promising biological activities like antibacterial, antiviral, antifungal, anticonvulsant, anti-cancer, hypoglycemic, antinociceptive and ulcerogenicity index [5-16]. They are cyclooxygenase inhibitors and therefore exhibit analgesic, anti-inflammatory activities [4,17].

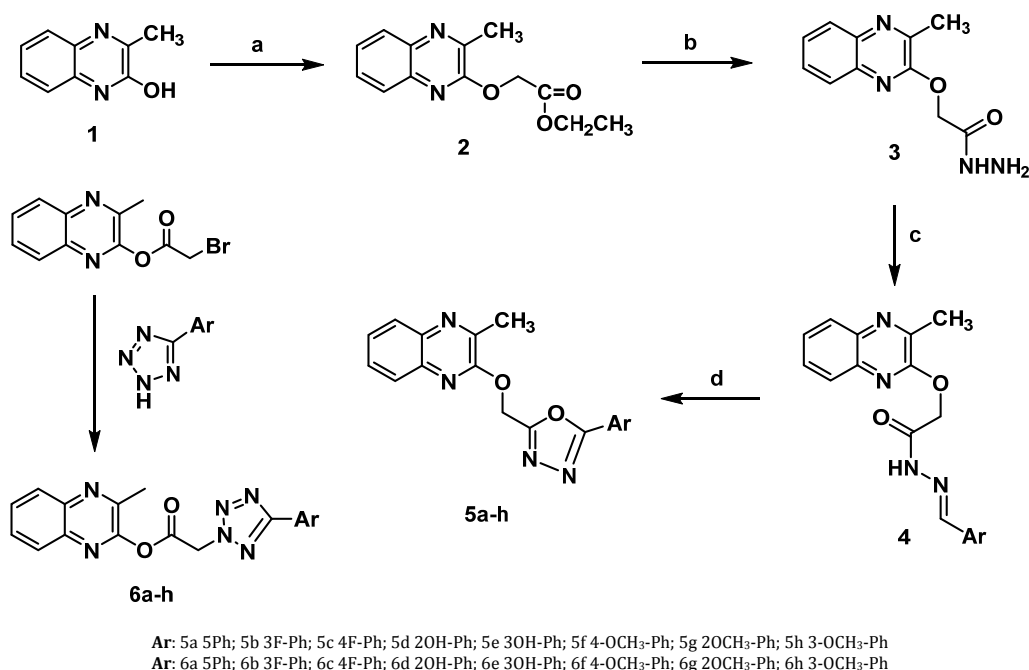
It was observed that several highly mutagenic and carcinogenic quinoxalines have been found in heated meat and fried fish. Some of the quinoxaline derivatives have been identified as mild hypo glycaemic agents and used for treating pain, epilepsy and other neurodegenerative disorders. Due to

DNA binding properties of quinoxalines, they show highest activity against the herpes virus.

They are part of well-known antibiotics such as levomycin, echinomycin, and actinoleutin that are known to inhibit growth of gram positive bacteria. Quinoxalines show various biological activities such as anti-viral, anti-depressant and as kinase inhibitors. They are active against transplantable tumors.

Fusion of tetrazole with quinoxalines is considered as planar acidic heterocyclic analogue of carboxylic function, which has the ability to increase potency and enhance bioavailability [18,19].

1,3,4-Oxadiazole is a neutral aromatic molecule which is thermally stable [20]. Quinoxalines containing 1,3,4-oxadiazole have been shown to possess a broad biological activity spectrum including antibacterial, antifungal, antiviral, anti-cancer, antihypertensive, anticonvulsant and anti-diabetic properties [20,21].



Reagents and conditions: a) C₂H₅OH, ethyl chloroacetate, dry K₂CO₃, reflux, 80 °C, overnight; b) Ethanol, NH₂NH₂, reflux, 80-90 °C, 5 hrs; c) RCHO, DMF, glacial acetic acid, reflux, 3 hr; d) Chloramine-T, ethanol, reflux, 80-90 °C, 5 hrs.; e) Aryl tetrazole, acetone, anhydrous K₂CO₃.

Scheme 1

Quinoxalines when fused with oxadiazole moiety was also identified as a Selective inhibitor of Guanylyl Cyclase (SGC) and important heme-site inhibitors for nitric oxide donor bioactivation. Moreover, the combined presence of quinoxaline and 1,3,4-oxadiazole in one frame are expected to show promising anti-inflammatory, analgesic and anticonvulsant activities.

Taking into account the importance of quinoxalines, tetrazoles and 1,3,4-oxadiazoles to both medicinal and heterocyclic chemistry, the following 2-((5-aryl-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline and 3-methyl quinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate are synthesized. The structures of the synthesized compounds were confirmed by IR, ¹H NMR, ¹³C NMR and Mass spectral data. All the synthesized derivatives were tested *in vitro* for their antibacterial activity.

2. Experimental

2.1. Instrumentations and reagents

All chemicals and reagents were of analytical grade and purchased from Merck. Solvents were used in purified form. For thin-layer chromatography (TLC) E. Merck AL silica gel 60F₂₅₄ plates were used and spots were visualized under UV light. Melting points were determined by using Mel-temp apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer (FT-IR) spectrometer. Only intense peaks are diagnosed and reported. ¹H NMR spectra were recorded using Varian NMR-400 MHz instrument. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. Signals are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); and coupling constants in Hz. Mass spectra were recorded with a PE Scienc model API 3000 mass spectrometer. All the reactions were carried out under the atmosphere of an inert gas, argon.

2.2. Synthesis

2.2.1. Synthesis of ethyl-2-(2-methylquinoxalin-3-yloxy)acetate (2)

3-Methyl quinoxalin-2-ol (0.01 mmol) was dissolved in ethanol (15 mL). To this solution ethylchloro acetate (0.01 mmol) and dry potassium carbonate (3 g) were added and refluxed at 80 °C for overnight. After the completion of reaction (monitored by TLC), the mixture was poured into ice cold water and filtered to separate the solid. The product was recrystallized from methanol (Scheme 1). Color: Yellow. Yield: 76%. M.p.: 196-198 °C. FT-IR (KBr, ν, cm⁻¹): 2943 (C-H), 1712 (C=O). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 7.80 (m, 2H, Ar-H), 7.68 (m, 2H, Ar-H), 5.21 (s, 2H, O-CH₂-C=O), 4.23 (q, 2H, O-CH₂-CH₃), 2.30 (s, 3H, N=CH-CH₃), 1.23 (t, 3H, O-CH₂-CH₃). MS (EI, m/z (%)): 246.1 (M+H).

2.2.2. Synthesis of 2-(2-methylquinoxalin-3-yloxy)acetate hydrazide (3)

To a solution of ethyl 2-(2-methylquinoxalin-3-yloxy)acetate (2) (0.01 mmol) in ethanol, was added hydrazine hydrate (99%, 20 mL) and refluxed for 5 h on a water bath at 80-90 °C. The reaction mixture was cooled and poured into crushed ice with stirring and kept aside for 30min for the precipitate to settle. The resultant precipitate was filtered, washed with water, dried and recrystallized from ethanol (Scheme 1). Color: Brown. Yield: 81%. M.p.: 204-206 °C. FT-IR (KBr, ν, cm⁻¹): 3532 (NH) 3011 (C-H) 1722 (C=O). ¹H NMR (400 MHz, DMSO-*d*₆, δ, ppm): 8.31 (d, 2H, Ar-H), 8.18 (d, 2H, Ar-H), 7.40 (brs, 1H, NH), 5.20 (s, 2H, O-CH₂), 4.70 (brs, 2H, NH₂), 2.31 (s, 3H, CH₃). MS (EI, m/z (%)): 232.1 (M+H)

2.2.3. Synthesis of *N'*-Arylidene-2-((3-methylquinoxalin-2-yl)oxy)acetohydrazides (4a-h)

A mixture of 2-(2-methylquinoxalin-3-yloxy)acetohydrazide (**3**) (0.01 mmol) and aldehyde (0.01 mmol) were dissolved in 25 mL of DMF and 2 mL of glacial acetic acid was added. This mixture was refluxed for 3h. After the completion of the reaction (monitored by TLC), reaction mixture was poured into crushed ice. Solid product thus obtained was filtered, washed with water and recrystallized from ethanol (Scheme 1).

N'-Benzylidene-2-((3-methylquinoxalin-2-yl)oxy)acetohydrazide (**4a**): Color: Brown. Yield: 76%. M.p.: 202-204 °C. FT-IR (KBr, ν , cm^{-1}): 3432 (NH) 3035 (C-H) 1718 (C=O). ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.21(brs, 1H, NH), 8.11(s, 1H, N=CH), 7.91 (m, 2H, Ar-H), 7.79 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 7.27 (m, 2H, Ar-H), 5.21 (s, 2H, O-CH₂), 2.30 (s, 3H, CH₃). MS (EI, m/z (%)): 320.13 (M+H).

N'-(3-Fluorobenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4b**): Color: White. Yield: 82%. M.p.: 204-206 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.25(brs, 1H, NH), 8.10(s, 1H, N=CH), 7.90 (m, 2H, Ar-H), 7.80 (m, 2H, Ar-H), 7.31 (m, 2H, Ar-H), 7.26 (m, 2H, Ar-H), 5.22 (s, 2H, O-CH₂), 2.35 (s, 3H, CH₃). MS (EI, m/z (%)): 339 (M+H).

N'-(4-Fluorobenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4c**): Color: light brown. Yield: 80%. M.p.: 202-204 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.26(brs, 1H, NH), 8.09(s, 1H, N=CH), 7.92 (m, 2H, Ar-H), 7.81 (m, 2H, Ar-H), 7.32 (m, 2H, Ar-H), 7.26 (m, 2H, Ar-H), 5.21 (s, 2H, O-CH₂), 2.33 (s, 3H, CH₃). MS (EI, m/z (%)): 339 (M+H).

N'-(2-Hydroxybenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4d**): Color: Light yellow. Yield: 78%. M.p.: 206-208 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 10.30 (brs, 1H, OH), 8.22 (brs, 1H, NH), 8.11 (s, 1H, N=CH), 7.91 (d, 2H, Ar-H), 7.80 (d, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 5.23 (s, 2H, O-CH₂), 2.35 (s, 3H, CH₃). MS (EI, m/z (%)): 337 (M+H).

N'-(3-Hydroxybenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4e**): Color: Light yellow. Yield: 76%. M.p.: 204-206 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 10.28 (brs, 1H, OH), 8.23 (brs, 1H, NH), 8.12 (s, 1H, N=CH), 7.93 (d, 2H, Ar-H), 7.82 (d, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.27 (m, 3H, Ar-H), 5.25 (s, 2H, O-CH₂), 2.32 (s, 3H, CH₃). MS (EI, m/z (%)): 337 (M+H).

N'-(4-Methoxybenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4f**): Color: White. Yield: 84%. M.p.: 200-202 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.24 (brs, 1H, NH), 8.11 (s, 1H, N=CH), 7.95 (d, 2H, Ar-H), 7.81 (d, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 5.22 (s, 2H, O-CH₂), 3.78 (s, 3H, OCH₃), 2.33 (s, 3H, CH₃). MS (EI, m/z (%)): 351 (M+H).

N'-(2-Methoxybenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4g**): Color: yellow. Yield: 80%. M.p.: 204-206 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.21 (brs, 1H, NH), 8.10 (s, 1H, N=CH), 7.98 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.29 (m, 2H, Ar-H), 5.23 (s, 2H, O-CH₂), 3.80 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃). MS (EI, m/z (%)): 351 (M+H).

N'-(3-Methoxybenzylidene)-2-((3-methyl quinoxalin-2-yl)oxy)acetohydrazide (**4h**): Color: Brown. Yield: 75%. M.p.: 204-206 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.22 (brs, 1H, NH), 8.10 (s, 1H, N=CH), 7.99 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 7.30 (m, 2H, Ar-H), 5.23 (s, 2H, O-CH₂), 3.79 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃). MS (EI, m/z (%)): 351 (M+H).

2.2.4. Synthesis of 2-(((3-methylquinoxalin-2-yl)oxy)methyl)-5-aryl-1,3,4-oxadiazole (5a-h)

A solution of *N'*-arylidene-2-((3-methylquinoxalin-2-yl)oxy)acetohydrazide (**4**) (0.01 mmol) and chloramine-T (0.05 mmol) in ethanol (25 mL) was refluxed for 5 h on a water bath at 80-90 °C. The reaction mixture was cooled and poured into crushed ice with stirring and kept aside for 30min for the

precipitate to settle down. The resultant precipitate was filtered, washed with water, dried and recrystallized from ethanol (Scheme 1).

2-(((5-Phenyl-1, 3, 4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5a**): Color: White. Yield: 79%. M.p.: 198-200 °C. FT-IR (KBr, ν , cm^{-1}): 2934 (C-H) 1422 (C=N). ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 7.90 (m, 1H, Ar-H), 7.8 (d, 1H, Ar-H), 7.74 (d, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 7.24 (m, 2H, Ar-H), 5.40 (s, 2H, O-CH₂), 2.30 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 168.02, 40.2, 135.1, 135.6, 132.4, 132.0, 130.3, 128.1, 126.6, 126.0, 125.9, 124.8, 123.2, 121.5, 118.4, 118.2, 71.1, 23.2. MS (EI, m/z (%)): 318.11 (M+H).

2-(((5-(3-Fluoro phenyl)-1, 3, 4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5b**): Color: Yellow. Yield: 78%. M.p.: 202-204 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 7.91 (m, 1H, Ar-H), 7.81 (m, 3H, Ar-H), 7.62 (m, 1H, Ar-H), 7.42 (m, 2H, Ar-H), 7.30 (m, 1H, Ar-H), 5.38 (s, 2H, O-CH₂), 2.31 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 168.2, 140.8, 138.9, 135.4, 135.2, 132.1, 1320.8, 130.1, 128.3, 128.1, 126.4, 126.3, 124.5, 123.6, 118.1, 70.6, 22.3. MS (EI, m/z (%)): 337 (M+H).

2-(((5-(4-Fluoro phenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5c**): Color: White. Yield: 68%. M.p.: 200-202 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 7.90 (m, 2H, Ar-H), 7.81 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 7.41 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 5.40 (s, 2H, O-CH₂), 2.30 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 168.1, 140.9, 138.9, 135.5, 135.3, 132.2, 130.9, 130.2, 128.4, 128.2, 126.5, 126.4, 124.6, 123.6, 118.1, 70.5, 23.0. MS (EI, m/z (%)): 337 (M+H).

2-(((5-(2-Hydroxy phenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5d**): Color: White. Yield: 69%. M.p.: 202-203 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 10.80 (brs, 1H, OH), 8.01 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H), 7.42 (m, 1H, Ar-H), 7.30 (m, 1H, Ar-H), 5.41 (s, 2H, O-CH₂), 2.31 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 168.2, 140.8, 139.0, 135.6, 135.4, 132.2, 140.0, 130.2, 128.5, 128.3, 126.5, 126.3, 124.5, 123.7, 118.2, 70.6, 22.9. MS (EI, m/z (%)): 335 (M+H).

2-(((5-(3-Hydroxy phenyl)-1, 3, 4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5e**): Color: Brown. Yield: 67%. M.p.: 206-208 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 10.78 (brs, 1H, OH), 7.99 (m, 2H, Ar-H), 7.89 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H), 7.42 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 5.42 (s, 2H, O-CH₂), 2.32 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 168.5, 140.9, 139.1, 135.8, 135.5, 132.4, 130.2, 130.0, 128.5, 128.3, 126.5, 126.2, 124.6, 123.7, 118.3, 71.0, 23.1. MS (EI, m/z (%)): 335 (M+H).

2-(((5-(4-Methoxy phenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5f**): Color: Yellow. Yield: 76%. M.p.: 208-210 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 7.98 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 7.43 (2H, Ar-H), 5.40 (s, 2H, Ar-H), 3.86 (s, 3H, O-CH₂), 2.31 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 167.2, 141.2, 139.5, 135.8, 136.5, 136.2, 134.5, 131.2, 130.8, 128.5, 128.2, 126.5, 126.1, 124.5, 123.8, 118.5, 70.8, 67.5, 23.2. MS (EI, m/z (%)): 349 (M+H).

2-(((5-(2-Methoxy phenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5g**): Color: Yellow. Yield: 80%. M.p.: 206-208 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 7.99 (m, 2H, Ar-H), 7.89 (m, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 7.42 (m, 2H, Ar-H), 5.40 (s, 2H, O-CH₂), 3.85 (s, 3H, OCH₃), 2.30 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 167.1, 141.2, 139.5, 136.5, 136.3, 134.6, 131.3, 130.8, 128.6, 128.3, 126.4, 126.1, 124.4, 123.8, 118.6, 70.8, 67.6, 23.1. MS (EI, m/z (%)): 349 (M+H).

2-(((5-(3-Methoxy phenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline (**5h**): Color: Yellow. Yield: 82%. M.p.: 206-208 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 8.00 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 7.42 (m, 2H, Ar-H), 5.39 (s, 2H, O-CH₂), 3.86 (s, 3H, OCH₃), 2.32 (s, 3H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 167.2, 141.3, 139.4, 136.5, 136.2, 134.5, 131.4, 130.8, 128.5, 128.2, 126.5, 126.0, 124.5, 123.8, 118.5, 70.7, 67.5, 23.0. MS (EI, m/z (%)): 349 (M+H).

Table 1. Anti-bacterial activity of 1,3,4-oxadiazole and tetrazole derivatives.

Compound	Ar	Gram negative		Gram positive	
		<i>E. coli</i> (ATCC 25922)	<i>P. aeruginosa</i> (ATCC 27853)	<i>S. aureus</i> (ATCC 12598)	<i>B. subtilis</i> (ATCC 6633)
Zones of inhibition of compounds in mm					
5a	5Ph	15	18	17	15
5b	3F-Ph	17	19	17	16
5c	4F-Ph	22	21	20	17
5d	2OH-Ph	17	17	16	15
5e	3OH-Ph	16	16	15	14
5f	4OCH ₃ -Ph	15	26	19	21
5g	2OCH ₃ -Ph	18	13	16	17
5h	3OCH ₃ -Ph	11	15	18	18
6a	5Ph	9	8	11	14
6b	3F-Ph	13	12	13	14
6c	4F-Ph	12	14	12	13
6d	2OH-Ph	15	26	24	19
6e	3OH-Ph	11	16	18	28
6f	4OCH ₃ -Ph	23	15	17	16
6g	2OCH ₃ -Ph	13	27	21	19
6h	3OCH ₃ -Ph	19	22	11	23
Gentamycin	-	35	36	30	35

2.2.5. Synthesis of 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate (6a-h)

A round-bottom flask equipped with a magnetic stirrer was charged with aryltetrazole (0.14 mmol) and acetone (25 mL). The suspension was cooled to 0 °C before adding anhydrous potassium carbonate. After stirring for 30 minutes at 0 °C, 3-methylquinoxalin-2-yl 2-bromoacetate (0.16 mmol) was added to the opaque mixture. The reaction was stirred for 16 h while slowly warming to room temperature. The mixture was filtered and thoroughly washed with additional acetone. The clear filtrate was concentrated under reduced pressure to give solid (Scheme 1).

3-Methylquinoxalin-2-yl-2-(5-phenyl-2H-tetrazol-2-yl)acetate (6a): Color: White. Yield: 80%. M.p.: 200-202 °C. FT-IR (KBr, ν , cm^{-1}): 3011 (C-H) 1248 (C=N). ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.16 (d, 1H, Ar-H), 7.95 (m, 1H, Ar-H), 7.81 (m, 3H, Ar-H), 7.58 (d, 2H, Ar-H), 7.32 (d, 1H, Ar-H), 7.28 (m, 1H, Ar-H), 5.40 (s, 2H, CO-CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.1, 159.5, 136.2, 134.4, 132.8, 130.1, 129.5, 128.0, 126.8, 126.5, 126.1, 125.9, 124.5, 122.1, 122, 119.8, 118.2, 66.5, 20.1. MS (EI, *m/z* (%)): 346.12 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(3-fluorophenyl)-2H-tetrazol-2-yl)acetate (6b): Color: Yellow. Yield: 82%. M.p.: 202-204 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.28 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.60 (d, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 5.42 (s, 2H, CO-CH₂), 2.28 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.2, 159.5, 159.0, 138.0, 136.1, 134.2, 130.1, 129.2, 128.8, 128.2, 127.8, 126.7, 126.2, 124.2, 119.4, 65.8, 19.8. MS (EI, *m/z* (%)): 365 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(4-fluorophenyl)-2H-tetrazol-2-yl)acetate (6c): Color: Yellow. Yield: 78%. M.p.: 202-204 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.26 (d, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.31 (m, 1H, Ar-H), 7.24 (m, 2H, Ar-H), 5.43 (s, 2H, CO-CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.1, 159.6, 159.2, 138.2, 136.2, 134.1, 130.2, 129.1, 128.8, 128.2, 127.8, 126.7, 126.6, 126.2, 124.1, 119.5, 66.0, 19.9. MS (EI, *m/z* (%)): 365 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(2-hydroxyphenyl)-2H-tetrazol-2-yl)acetate (6d): Color: Brown. Yield: 82%. M.p.: 204-206 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 10.81 (brs, 1H, OH), 8.18 (d, 2H, Ar-H), 7.66 (d, 1H, Ar-H), 7.56 (d, 2H, Ar-H), 7.26 (m, 1H, Ar-H), 7.31 (m, 1H, Ar-H), 7.24 (m, 1H, Ar-H), 5.43 (s, 2H, CO-CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.2, 160.1, 159.2, 139.5, 136.5, 134.0, 130.5, 130.2, 129.0, 128.5, 127.6, 126.5, 126.1, 124.0, 118.5, 66.5, 21.5. MS (EI, *m/z* (%)): 363 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(3-hydroxyphenyl)-2H-tetrazol-2-yl)acetate (6e): Color: Yellow. Yield: 84%. M.p.: 204-206 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 10.84 (brs, 1H, OH), 8.16 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H), 7.55 (m, 2H, Ar-H), 7.35 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 5.41 (s, 2H, CO-CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.3, 160.2, 159.6, 139.6, 136.6, 134.2, 130.6, 130.1, 129.3, 128.6, 127.6, 126.6, 126.1, 124.2, 119.6, 66.8, 21.5. MS (EI, *m/z* (%)): 363 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(4-methoxyphenyl)-2H-tetrazol-2-yl)acetate (6f): Color: Yellow. Yield: 80%. M.p.: 210-212 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.16 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 5.40 (s, 2H, CO-CH₂), 3.84 (s, 3H, OCH₃), 2.31 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 175.1, 161.3, 159.5, 140.3, 136.5, 134.5, 130.7, 130.2, 129.8, 128.6, 127.9, 126.5, 126.1, 124.8, 120.3, 68.9, 22.6. MS (EI, *m/z* (%)): 377 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(2-methoxyphenyl)-2H-tetrazol-2-yl)acetate (6g): Color: Yellow. Yield: 76%. M.p.: 210-212 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.15 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.60 (m, 2H, Ar-H), 7.40 (m, 2H, Ar-H), 5.41 (s, 2H, CO-CH₂), 3.82 (s, 3H, OCH₃), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.3, 161.2, 159.5, 140.4, 136.5, 134.5, 130.8, 130.2, 129.8, 128.5, 127.9, 126.6, 126.2, 124.8, 120.2, 68.9, 22.5. MS (EI, *m/z* (%)): 377 (M+H).

3-Methylquinoxalin-2-yl-2-(5-(3-methoxyphenyl)-2H-tetrazol-2-yl)acetate (6h): Color: Yellow. Yield: 78%. M.p.: 210-212 °C. ¹H NMR (400 MHz, DMSO-*d*₆, δ , ppm): 8.14 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.58 (m, 2H, Ar-H), 7.40 (m, 2H, Ar-H), 5.40 (s, 2H, CO-CH₂), 3.83 (s, 3H, OCH₃), 2.31 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆, δ , ppm): 174.5, 161.3, 159.5, 140.5, 136.6, 134.6, 131.2, 130.8, 130.2, 129.8, 128.8, 127.9, 127.1, 126.3, 125.2, 120.5, 69.0, 65.4, 22.3. MS (EI, *m/z* (%)): 377 (M+H).

2.2.6. Anti-bacterial activity

Agar well diffusion method was used to determine the anti-microbial activity of synthesized compounds, 2-((5-aryl-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxalines and 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetates. All the compounds were tested against Gram positive strains (*Staphylococcus aureus* (ATCC 12598) and *Bacillus subtilis* (ATCC 6633)) and Gram negative strains (*Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and standard anti-bacterial drug Gentamycin is used as reference drug (Table 1).

3. Results and discussions

Taking into account the importance of quinoxalines, tetrazoles and 1,3,4-oxadiazoles to both medicinal and heterocyclic chemistry, 2-((5-aryl-1,3,4-oxadiazol-2-yl) methoxy)-3-methyl quinoxaline and 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate derivatives are synthesized from *N'*-Arylidene-2-((3-methylquinoxalin-2-yl)oxy)acetohydrazide. The structures of the synthesized compounds were confirmed by ¹H NMR, ¹³C NMR and Mass spectral data. They have been screened for their antibacterial activity against four pathogenic strains.

The screening results of antibacterial activity of 1,3,4-oxadiazole and tetrazole derivatives **5a-f** and **6a-f** are summarized in Table 1. Compounds **5c**, **6d** and **6g** show moderate activity in the range of 20-24 mm against *S. aureus*. Compounds **5f** and **6h** exhibit moderate activity against *B. subtilis*. Compounds **5c** and **6f** against *E. coli* and compounds **5c** and **6h** against *P. aeruginosa*. Compounds **5f**, **6d** and **6g** exhibit excellent activity in the range of 25-28 mm against *P. aeruginosa*. Compound **6e** shows appreciable activity against *B. subtilis*.

4. Conclusion

Herein we reported the synthesis of some new, 2-((5-aryl-1,3,4-oxadiazol-2-yl)methoxy)-3-methyl quinoxaline and 3-methylquinoxalin-2-yl-2-(5-aryl-2H-tetrazol-2-yl)acetate derivatives and recorded their antibacterial activity.

Acknowledgements

Authors are thankful to management, Principal and Head, Department of Sciences and Humanities, Geethanjali College of Engineering and Technology for their encouragement and support for doing the research work.

References

- [1]. Bekhit, A. A.; El-Sayed, O. A.; El-Sayed, A.; Park, J. Y. *Eur. J. Med. Chem.* **2004**, *39*, 249-255.
- [2]. Smita, S.; Sharma, M. C.; Kohli, D. V. *J. Optoelect. Biomed. Mat.* **2010**, *1(3)*, 151-160.
- [3]. Mohite, P. B.; Bhaskar, V. H. *Int. J. Pharm. Tech. Res.* **2011**, *3*, 1557-1566.
- [4]. Wagle, S.; Adhikari, A. V.; Kumari, S. K. *Eur. J. Med. Chem.* **2009**, *44*, 1135-1143.
- [5]. Upadhayaya, R. S.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R.; Arora, S. K. *Eur. J. Med. Chem.* **2004**, *39*, 579-592.
- [6]. Matysiak, J.; Niewiadomy, A.; Krajewska-Kulak, E.; Niewiadomy, M. G. *Il Farmaco* **2003**, *58*, 455-461.
- [7]. Popat, B. M.; Vaidhun, H. B. *Orbital-Elec. J. Chem.* **2010**, *3*, 311-315.
- [8]. Rajasekaran, A.; Thampi, P. P. *Eur. J. Med. Chem.* **2004**, *39*, 273-279.
- [9]. Rajasekaran, A.; Thampi, P. P. *Eur. J. Med. Chem.* **2005**, *40*, 1359-1364.
- [10]. Bhaskar, V. H.; Mohite, P. B. *J. Optoelect. Biomed. Mat.* **2010**, *2(4)*, 249-259.
- [11]. Pattan, S. R.; Kekare, P.; Patil, A.; Nikalge, A.; Kittur, B. S. *Iran J. Pharm. Sci.* **2009**, *5(4)*, 225-230.
- [12]. Basheer, H. A.; Aveen, A. I.; Mayssoon, S. A. *J. Pure Appl. Chem.* **2016**, *2(1)*, 1-3.
- [13]. Navidpour, L.; Amini, M.; Shafaroodi, H.; Abdi, K.; Ghahremani, M. H.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2006**, *15*, 4483-4487.
- [14]. Gao, Y. L.; Zhao, G. L.; Liu, W.; Shao, H.; Wang, Y. L.; Xu, W. R.; Tangand, L. D.; Wang, J. W. *Indian J. Chem. B* **2010**, *49*, 1499-1508.
- [15]. Rajasekaran, A.; Rajagopal, K. A. *Acta Pharm.* **2009**, *59*, 355-364.
- [16]. Gundugola, A. S.; Chandra, K. L.; Perchellet, E. M.; Water, A. M.; Rayat, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3920-3924.
- [17]. Sharon, A.; Pratap, R.; Tiwari, P.; Srivastava, A.; Maulik, P. R.; Vishnu, J. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2115-2117.
- [18]. Umarani, N.; Kaliappan, I.; Singh, N. K. *Derpharma Chem.* **2010**, *2(1)*, 159-167.
- [19]. Umarani, N. K. *Int. J. Pharm. Sci. Rev. Res.* **2010**, *2(2)*, 24-28.
- [20]. Othman, A. A.; Mebrouk, K.; Sarah, A. *Arab. J. Chem.* **2014**, *32*, 714-725.
- [21]. Oliveira, C. S.; Lira, B. F.; Barbosa-Filho, J. M.; Lorenzo, J. G. F.; Athayde-Filho, P. F. *Molecules* **2012**, *17*, 10192-10231.