A facile synthesis of 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)quinoxaline-2-carboxamides and N-(3-chloro-2-oxo-4-arylazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamides

V Haripriya\textsuperscript{a,b}, E Laxminarayana\textsuperscript{a} & M Thirumala Chary\textsuperscript{a,b}
\textsuperscript{a}SR Engineering College(Autonomous), Ananthasagar, Hasnapathy, Warangal 506 371, India
\textsuperscript{b}Jawaharlal Nehru Technological University Hyderabad College of Engineering, Nachupally, Karimnagar 505 501, India
\textsuperscript{c}Mahatma Gandhi Institute of Technology, Gandipet, Hyderabad 500 075, India
E-mail: mtcharya@yahoo.com

Received 29 August 2013; accepted (revised) 2 July 2014

o-Phenylenediamine reacts with diethylbromo malonate to form ethyl-1,2,3,4-tetrahydro-3-oxoquinoxaline-2-carboxylate 2, which reacts with hydrazinehydrate to form 3-hydroxyquinoxaline-2-carbohydrazide 3. Compound 3 on condensation with different aromatic aldehydes gives N-arylidenene-3-hydroxyquinoxaline-2-carbohydrazides 4 which is cyclised with chloroacetyl chloride and thioglycolic acid to obtain N-(3-chloro-2-oxo-4-arylazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamides \textsuperscript{5} and 3-hydroxy-N-(4-oxo-2-phenylthiazolidin-3-yl)quinoxaline-2-carboxamides \textsuperscript{6} respectively. The structures of these compounds are confirmed by \textsuperscript{1}H NMR and LC-MS data.

Keywords: Quinoxaline, phenylenediamine, arylidine, azetidinone, thiazolidinone

Quinoxaline derivatives are an important class of compounds that find use in medicinal chemistry\textsuperscript{1-4}. For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit growth of gram negative bacteria\textsuperscript{2}, and are active against various transplatable tumors\textsuperscript{3}.

Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 2-diamines with α-diketones\textsuperscript{5}, 1,4-addition of 1,2-diamines to diazenylbutenes\textsuperscript{6}, cyclization-oxidation of phenacyl bromides\textsuperscript{7} and oxidative coupling of epoxides with ene-1,2-diamines\textsuperscript{8}. 2,3-Disubstituted quinoxalines have also been prepared via the Suzuki-Miyaura coupling reaction\textsuperscript{9}, condensation of o-phenylenediamines with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation\textsuperscript{10}, and iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds with substituted o-phenylenediamines in DMF (Ref. 11) or CH\textsubscript{3}CN (Ref. 12). Also, α-hydroxy ketones react with o-phenylenediamines in the presence of transition metals such as Mn, Pd, Ru and Cu, Pb to give quinoxalines\textsuperscript{8,13}.

Recently we reported synthesis of quinoxaline derivatives\textsuperscript{4}. We report herein synthesis of quinoxalines using of o-phenylenediamine and bromoethyl-acetoacetate as reactants. As outlined in Scheme I, the reaction of o-phenylenediamine and bromoethyl-acetoacetate gave only compounds 2 and it is converted to hydrazine derivative 3, from which arylidine derivatives 4 were synthesized. The arylidine derivatives are converted into corresponding azetidinones 5 and thiazolidinones 6.

**Experimental Section**

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point (Buchi B-540) apparatus and are uncorrected. The \textsuperscript{1}H NMR spectra were recorded in the indicated solvent on a Varian 400 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm with TMS as internal standard. Mass spectra were measured on a Jeol JMS D-300 spectrometer. The homogeneity of the compounds was checked using precoated TLC plates (E. Merck Kieselgel 60 F\textsubscript{254}).

**Ethyl-1,2,3,4-tetrahydro-3-oxoquinoxaline-2-carboxylate, 2.** Mixture of compound 1 (1 g, 9.25 mmol, 2 eq.) and diethyl 2-bromomalonate (1.1 g, 4.60 mmol, 2 eq.) was stirred under vacuum for 8 hr. After completion of the reaction (checked by TLC), solid mass was purified by silica gel column chromatography using 20-60% EtOAc in pet. ether. The structure of the compound was confirmed by \textsuperscript{1}H NMR and LC-MS data. Yield: 600 mg (60%); Off white solid, m.p. 226°C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz): δ 1.21 (t, 3H), 4.2 (q, 2H), 4.57 (s, 1H), 4.60 (s, 1H), 6.70 (d, 1H), 6.80 (t, 2H), 6.95 (d, 1H), 7.90 (s, 1H); LC-MS: m/z 220 (M\textsuperscript{+}) purity-99%.

**3-Hydroxyquinoxaline-2-carbohydrazide, 3.** To a stirred solution of compound 2 (600 mg, 2.72 mmol, 1 eq) in EtOH (10 mL) 50-60% of hydrazine hydrate (270 mg, 8.45 mmol, 2 eq.) was added at RT and the reaction mixture was refluxed for 2 hr. After completion of the reaction (checked by TLC),
reaction mixture was allowed to cool to RT, resultant solid was filtered and dried. The structure of the compound was confirmed by \( ^1\)H NMR and LC-MS data. Yield: 500 mg (90%); Yellow solid, m.p. 224°C.

\( ^1\)H NMR (DMSO-\( d_6\), 400 MHz): \( \delta \) 5.80 (brs, 1H), 7.38 (d, 2H), 7.68 (d, 2H), 8.02 (brs, 2H), 9.80 (brs, 1H); LC-MS: \( m/z \) 204 (M\(^+\)) purity-84%.

\( \text{N'}-\text{Arylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4a.} \) To a stirred solution of compound 3 (500 mg, 2.45 mmol, 1 eq) in EtOH (10 mL) 2-methylbenzaldehyde (309 mg, 2.57 mmol, 1.05 eq.) and catalytic amount of conc. HCl were added at RT and the reaction mixture was stirred at RT for 1 hr. After completion of the reaction (checked by TLC). The mixture was diluted with water, basified with sat. aq. NaHCO\(_3\) and resultant solid was filtered, washed with water and dried. The structure of the compound was confirmed by \( ^1\)H NMR and LC-MS data. Other members of this series were also prepared using this procedure. Yield: 600 mg (80%); Yellow solid
**N-(3-Chloro-2-oxo-4-arylazetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamides, 5a.** To a stirred solution of compound 4 (200 mg, 0.65 mmol, 1 eq) in DMF (3 mL) Et3N (0.2 mL, 4.70 mmol, 3 eq.) chloroacetyl chloride (109 mg, 0.97 mmol, 1.43 eq.) was added at 0°C and the reaction mixture was stirred at RT for 2 hr. After completion of the reaction (checked by TLC), the reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with water and brine, dried over anhydrous Na2SO4 and concentrated. Crude material was purified by silica-gel column chromatography using 10-30% EtOAc in pet ether. The structure of the compound was confirmed by LC-MS data. Other members of this series are prepared using this procedure.

**N-(3-Chloro-2-oxo-4-(2-methylphenyl)azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5b.** 1H NMR (DMSO-d6, 400 MHz): δ 9.51 (brs, 1H), 8.28 (brs, 1H), 8.05-7.90 (m, 2H), 7.82 (d, 1H), 7.70-7.58 (m, 3H), 7.55 (d, 2H), 6.81 (d, 1H, J = 5.6 Hz), 6.38 (d, 1H, J = 5.6Hz), 2.41(s, 3H); MS: m/z 382 (M+), m.p. 236°C.

**N-(3-Chloro-2-oxo-4-(2-chlorophenyl)azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5c.** 1H NMR (DMSO-d6, 400 MHz): δ 9.45 (brs, 1H), 8.12 (brs, 1H), 8.04-7.91 (m, 2H), 7.79 (d, 1H), 7.70-7.49 (m, 3H), 7.52 (d, 2H), 6.82 (d, 1H, J = 5.5 Hz), 6.37 (d, 1H, J = 5.5Hz); MS: 402 (M+), m.p. 234°C.

**N-(3-Chloro-2-oxo-4-(3-methoxyphenyl)azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5d.** 1H NMR (DMSO-d6, 400 MHz): δ 9.50 (brs, 1H), 8.29 (brs, 1H), 8.05-7.91 (m, 2H), 7.83(d, 1H), 7.71-7.49 (m, 3H), 7.57 (d, 2H), 6.80 (d, 1H, J = 5.6 Hz), 6.39 (d, 1H, J = 5.6Hz), 3.76(s, 3H); MS: m/z 398 (M+), m.p. 240°C.

**N-(3-Chloro-2-oxo-4-(2-nitrophenyl)azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5e.** 1H NMR (DMSO-d6, 400 MHz): δ 9.45 (brs, 1H), 8.21 (brs, 1H), 8.06-7.91 (m, 2H), 7.81 (d, 1H), 7.69-7.59 (m, 3H), 7.57 (d, 2H), 6.82 (d, 1H, J = 5.6 Hz), 6.41 (d, 1H, J = 5.6 Hz); MS: m/z 413 (M+), m.p. 245°C.

**3-Hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)quinoxaline-2-carboxamides, 6a.** To a stirred solution compound 4 (200 mg, 0.65 mmol, 1 eq) in DMF (3 mL) ZnCl2 (3 eq.) thioglycolic acid (0.97 mmol, 1.5 eq.) were added at 0°C and the reaction mixture was stirred at RT for 2 hr. After completion of the reaction (checked by TLC), the reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with water and brine, dried over anhydrous Na2SO4 and concentrated. Crude material was purified by silica-gel column chromatography using 10-30% EtOAc in pet ether. The structure of the compound was confirmed by LC-MS data. Other members of these series are prepared using this procedure.

**3-Hydroxy-N-(4-oxo-2-methylphenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6a.** 1H NMR (DMSO-d6, 400 MHz): δ 9.42 (brs, 1H), 8.08 (brs, 1H), 7.81 (d, 2H), 7.72 (d, 1H), 7.60 (d, 1H), 7.38-7.21 (m, 3H), 7.19 (d, 1H), 6.21 (s, 1H), 3.19 (dd, 2H), 2.40 (s, 3H); MS: m/z 380 (M+), m.p. 239°C.

**3-Hydroxy-N-(4-oxo-2-chlorophenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6b.** 1H NMR (DMSO-d6, 400 MHz): δ 9.48 (brs, 1H), 8.12 (brs, 1H), 7.83 (d, 2H), 7.73 (d, 1H), 7.61 (d, 1H), 7.39-7.23 (m, 3H), 7.21 (d, 1H), 6.18 (s, 1H), 3.20 (dd, 2H); MS: m/z 400 (M+), m.p. 234°C.

**3-Hydroxy-N-(4-oxo-3-methoxyphenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6c.** 1H NMR (DMSO-d6, 400 MHz): δ 9.52 (brs, 1H), 8.10 (brs, 1H), 7.80 (d, 2H), 7.71 (d, 1H), 7.60 (d, 1H), 7.38-7.22 (m, 3H), 7.20 (d, 1H), 6.24 (s, 1H), 3.22 (dd, 2H), 3.82 (s, 3H); MS: m/z 396 (M+), m.p. 244°C.

**3-Hydroxy-N-(4-oxo-2-nitrophenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6d.** 1H NMR (DMSO-d6, 400 MHz): δ 9.65 (brs, 1H), 8.20 (brs, 1H), 7.86 (d, 2H), 7.76 (d, 1H), 7.65 (d, 1H), 7.42-7.26 (m, 3H), 7.25 (d, 1H), 6.20 (s, 1H), 3.18 (dd, 2H); MS: m/z 411 (M+), m.p. 248°C.

**3-Hydroxy-N-(4-oxo-3-nitrophenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6e.** 1H NMR (DMSO-d6, 400 MHz): δ 9.63 (brs, 1H), 8.22 (brs, 1H), 7.85 (d, 2H), 7.75 (d, 1H), 7.64 (d, 1H), 7.41-7.26 (m, 3H), 7.24 (d, 1H), 6.20 (s, 1H), 3.21 (dd, 2H); MS: m/z 411 (M+), m.p. 244°C.

**Acknowledgement**

One of the authors Haripriya (SR/WOS-A/CS-100) is thankful to DST, Ministry of Science and Technology, New Delhi, India, Management and Principal of SR engineering college (Autonomous), Warangal for financial support and encouragement.

**References**