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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

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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-hydroxy-quinoxaline-2-carbohydrazide **3**. Compound **3** on condensation with different aromatic aldehydes gives *N*'-arylidene-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 **5** and 3-hydroxy-N-(4-oxo-2-phenylthiazolidin-3-yl)quinoxaline-2-carboxamides **6** respectively. The structures of these compounds are confirmed by ^{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[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 positive bacteria[2], and are active against various transplantable tumors[3].

Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1,2-diamines with α-diketones[5], 1,4-addition of 1,2-diamines to diazenylbutenes[6], cyclization-oxidation of phenacyl bromides[7] and oxidative coupling of epoxides with ene-1,2-diamines[8]. 2,3-Disubstituted quinoxalines have also been prepared via the Suzuki-Miyaura coupling reaction[9], condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation[10], and iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds with substituted *o*-phenylenediamines in DMSO (Ref. 11) or CH_3CN (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[8,13].

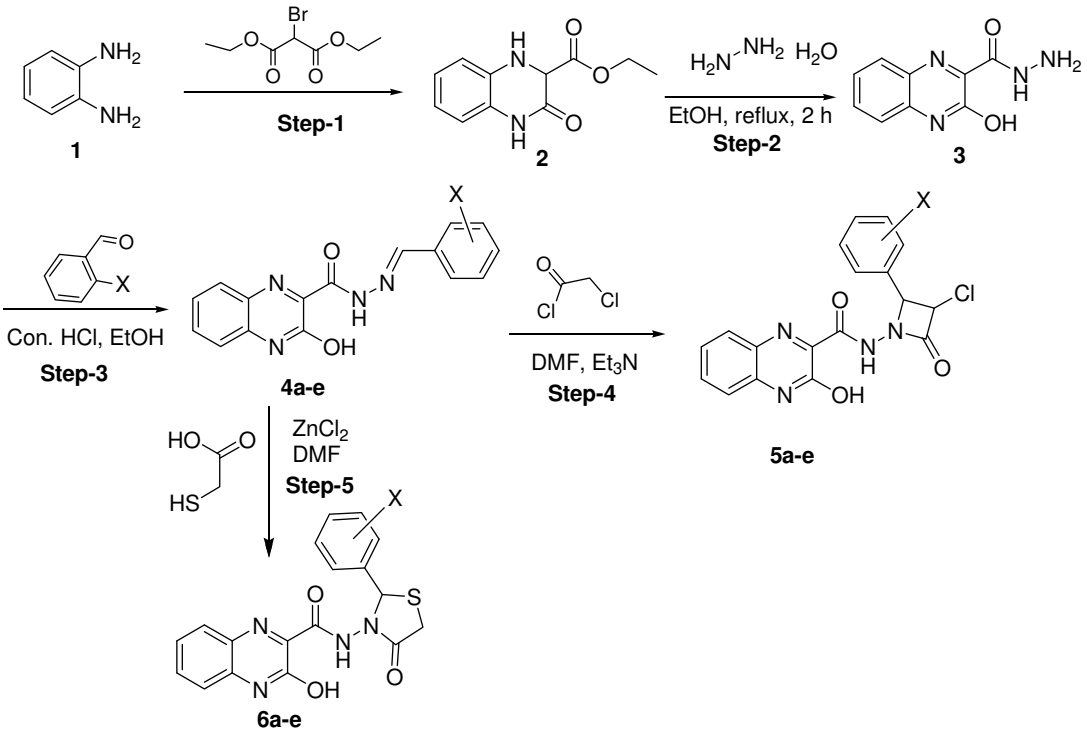
Recently we reported synthesis of quinoxaline derivatives[4]. We report herein synthesis of quinoxalines using of *o*-phenylenediamine and bromoethyl-acetoacetate as reactants. As outlined in **Scheme I**, the reaction of *o*-phenylenediamine and bromoethyl-acetoacetate gave only compounds **2** and 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 ^{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_{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 ^{1}H NMR and LC-MS data. Yield: 600 mg (60%); Off white solid, m.p. 226°C. ^{1}H NMR (DMSO-d_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^+) 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),



Compd	X	Compd	X
5a	2-CH_3	**6a**	2-CH_3
5b	2-Cl	**6b**	2-Cl
5c	3-OCH_3	**6c**	3-OCH_3
5d	2-NO_2	**6d**	2-NO_2
5e	3-NO_2	**6e**	3-NO_2

Scheme I

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): δ 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%.

***N′*-Arylidene-3-hydroxyquinoxaline-2-carbo-hydrazides, 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′*-Arylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4a**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.15 (s, 3H), 7.18-7.79 (m, 8H), 8.05 (s, 1H), 8.51 (brs, 1H), 12.01 (brs, 1H); LC-MS: *m/z* 306 (M^+), m.p. 228°C

***N′*-2-Methylphenylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4b**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.20-7.80 (m, 8H), 8.02 (s, 1H), 8.42 (brs, 1H), 12.03 (brs, 1H); MS: *m/z* 326 (M^+), m.p. 230°C

***N′*-Arylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4c**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.86 (s, 3H), 7.15 (s, 1H), 7.19-7.89 (m, 8H), 7.99 (s, 1H), 8.48 (brs, 1H), 11.90 (brs, 1H); MS: *m/z* 322 (M^+), m.p. 232°C

***N′*-Arylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4d**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.40-7.79 (m, 8H), 8.04 (s, 1H), 8.50 (brs, 1H), 12.56 (brs, 1H); MS: *m/z* 337 (M^+), m.p. 238°C

***N′*-Arylidene-3-hydroxyquinoxaline-2-carbohydrazide, 4e**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.38-7.80 (m, 8H), 8.05 (s, 1H), 8.48 (brs, 1H), 12.01 (brs, 1H); MS: *m/z* 337 (M^+), m.p. 240°C

***N*-(3-Chloro-2-oxo-4-arylazetidin-1-yl)-3-hydroxy-quinoxaline-2-carboxamides, 5a**. To a stirred solution of compound **4** (200 mg, 0.65 mmol, 1 eq) in DMF (3 mL) Et_3N (0.2 mL, 4.70 mmol, 3 eq.) chloro acetylchloride (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), reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 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, 5a**. ^{1}H NMR (DMSO-d_6, 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* = 5.6Hz), 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 5b**. ^{1}H NMR (DMSO-d_6, 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* = 5.5Hz), 6.37 (d, 1H, *J* = 5.5Hz); MS: 402 (M^+), m.p. 238°C

***N*-(3-Chloro-2-oxo-4-(3-methoxyphenyl)-azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5c**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.48 (brs, 1H), 8.31(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, 5d**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.50 (brs, 1H), 8.29 (brs, 1H), 8.04-7.92 (m, 2H), 7.83 (d, 1H), 7.71-7.59 (m, 3H), 7.56 (d, 2H), 6.82 (d, 1H, *J* = 5.6 Hz), 6.40 (d, 1H, *J* = 5.6 Hz); MS: *m/z* 413 (M^+), m.p. 246°C

***N*-(3-Chloro-2-oxo-4-(3-nitrophenyl)azetidin-1-yl)-3-hydroxyquinoxaline-2-carboxamide, 5e**. ^{1}H NMR (DMSO-d_6, 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. 248°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) $ZnCl_2$ (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 Na_2SO_4 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.

3-Hydroxy-*N*-(4-oxo-2-methylphenylthiazolidin-3-yl)quinoxaline-2-carboxamide, 6a. ^{1}H NMR (DMSO-d_6, 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. ^{1}H NMR (DMSO-d_6, 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. ^{1}H NMR (DMSO-d_6, 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. ^{1}H NMR (DMSO-d_6, 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. ^{1}H NMR (DMSO-d_6, 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

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