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Synthesis and antibacterial activity of 3,4-dihydroquinoxalin-2(1*H*)-one derivatives

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ABSTRACT

*The quinoxalinone skeleton is used as an intermediate in designing novel quinoxalinone derivatives with potential as novel anticancer, antimicrobial, antifungal, antithrombotic and antianxiolytic agents and glycogen phosphorlyase inhibitors, and also as fluoroionophores. The present paper describes the synthesis and antibacterial activity of some novel 3,4-dihydroquinoxalin-2H-(1H)-one derivatives **5a-5j** (**Scheme 1**) from commercially available 1,2-phenylenediamine as starting material. The newly synthesized compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display good to moderate antibacterial activity against all the tested bacterial strains. It was observed that among all the compounds tested, compound **5i** exhibited equipotent activity and **5j** showed good activity (having fluorine substituent) against all the tested bacterial strains and the remaining compounds such as compounds **5a, 5b, 5c, 5d** and **5e** having methyl and methoxy substituents displayed moderate activity while the compounds **5f, 5g** and **5h** showed no activity.*

Keywords: Antibacterial activity, 3,4-Dihydroquinoxalin-2H-(1H)-one, 1,2-Phenylenediamine, Synthesis

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INTRODUCTION

Quinoxalines including their fused-ring derivatives are relatively easy to prepare [1-2] and many of such derivatives have been reported to display diverse pharmacological activities [3-5] Quinoxaline ring system represents the building block of many biologically active compounds that possess anti-inflammatory [6,7], antibacterial [8-10], antifungal [11], anticancer [12,13], antimalarial [14], CNS depressant [15] and hypoglycemic [16] activities. The quinoxalinone skeleton is used as an intermediate in designing novel quinoxalinone derivatives with potential as novel anticancer, antimicrobial, antifungal, antithrombotic and antianxiolytic agents and glycogen phosphorlyase inhibitors, and also as fluoroionophores [17]. The present paper describes the synthesis and antibacterial activity of some novel 3,4-dihydroquinoxalin-2H-(1H)-one derivatives **5a-5j** (**Scheme 1**) from commercially available 1,2-phenylenediamine as starting material.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV

light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (400MHz). The ^{13}C NMR spectra recorded in $CDCl_3$ on a Varian EM-360 spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. All the reactions were carried out under argon atmosphere.

Experimental methods

Synthesis of 3, 4-dihydroquinoxalin-2(1H)-one **(2)**

A mixture of o-phenylenediamine (10.0 g, 92 mmol), chloroacetic acid (8.7 g, 92 mmol) in aqueous ammonia (33 %, 10 mL) in water (80 mL) was bmbmmbmbb to reflux temperature for one hour. On cooling light brown solid was precipitated and was filtered under reduced pressure and dried at 110 °C, to obtain off white solid. M.p: 134-136 °C; Yield; 83 % ; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.99 (s, 2 H), 6.68 (d, *J* = 6.0 Hz, 1H), 6.75 (d, *J* = 3.2 Hz, 2H), 6.90-6.87 (m, 1 H), 8.78 (br.s, 1H); ESI-MS: m/z (rel.abund.%) 149 (M+1).

Synthesis of 4-(2-chloroacetyl)-3,4-dihydroquinoxalin-2(1H)-one **(3)**

Chloroacetyl chloride (2.9 mL, 37 mmol) was added drop wise to the ice cold solution of 3,4-dihydroquinoxalin-2(1*H*)-one **2** (5.0 gm, 34 mmol) in dry DMF (20 mL). After addition, the solution was stirred at room temperature for one hour. The contents of the reaction flask were then poured slowly into aqueous solution of sodium bicarbonate (6%, 100 mL) with continuous stirring and the resulting precipitates were filtered, washed and dried in oven at 110 °C to obtain compound **3** as off white solid. M.p. 194-196 °C, Yield: 74%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.60 (s, 2 H), 4.60 (s, 2H), 7.60-7.20 (m, 4H), 10.48 (br.s, 1H).

Synthesis of 1-(2-(4-bromophenyl)-2-oxoethyl)-4-(acetyl chloride)-3,4-dihydroquinoxalin-2(1H)-one **(4)**

A mixture of compound compound **3** (2.5 g, 11.1 mmol), 4-bromo phenacyl bromide (3.09 g, 11.1 mmol), K_2CO_3 (3.06 g, 22.2 mmol) in CH_3CN (20 mL) was refluxed at 90 ^oC for 10 h. The resulting precipitate was filtered, thoroughly washed with water and dried to obtain compound **4**. Off white solid, M.p.: 249-252 °C, Yield: 75%.

General experimental procedure for the synthesis of novel 3,4-dihydroquinoxalin-2(1H)-one derivatives 5a – 5j

To a stirred suspension of compound **4** (200 mg, 0.475 mmol) and $NaHCO_3$ (80 mg, 0.95 mmol) in 2-propanol (15 mL) was added anilines **a – j** (0.475 mmol) followed by potassium iodide (20 mol%). The reaction mixture was refluxed for eight to twelve hours. The progress of the reaction was monitored by TLC analysis (40% Ethylacetate-n-Hexane). After completion of the reaction, the reaction mixture was cooled to room temperature and filtered to remove the inorganic salts. The solvent was removed under reduced pressure and the pure compounds **5a**-**5j** were obtained by column chromatography using 30% ethylacetate: n-Hexane. Yields of the products vary from 50-77%.

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(phenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5a:**

Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3417, 2930, 1740, 1677, 1602, 1585, 1504, 1382, 1292, 1221, 1071, 972, 813, 750, 696 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.20 (s, 2 H), 4.60 (s, 2H), 5.50 (s, 2H), 5.88 (br.s 1H), 6.64-6.62 (m, 3H), 7.60-6.90 (m, 5H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.80 (d, *J* = 10.4 Hz, 1H), 8.01 (d, *J* = 10.4 Hz, 1H); ESI-MS: m/z (rel.abund.%) 478 (M+), 480 (M+2).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(3-methoxyphenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5b:**

Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3369, 2926, 2853, 1678, 1585, 1502,1466, 1381, 1216, 1071, 1040, 979, 814, 754, 687 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 3.80 (s, 3H), 4.10 (s, 2 H), 4.54 (s, 2H), 5.50 (s, 2H), 6.12 (d, *J* = 10.0 Hz, 2H), 6.98 (t, *J* = 9.2 Hz, 1H), 7.58-7.0 (m, 4H), 7.69 (d, *J* = 9.2 Hz, 2H), 7.80 (d, *J* = 11.2 Hz, 2H), 8.03 (d, *J* = 9.2 Hz, 2H); ESI-MS: m/z (rel.abund.%) 508 (M+, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(4-methoxyphenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5c:**

Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 2926, 2854, 1739, 1661, 1585, 1465, 1379, 1229, 1071, 980, 815,752 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 3.80 (s, 3 H), 4.20 (s, 2 H), 4.60 (s, 2H), 5.58-5.50 (m, 3H), 6.50 (br, 1H), 7.35-7.01 (m, 5H), 7.68 (d, *J* = 10.4 Hz, 1H), 7.80 (d, *J* = 10.8 Hz, 2H), 8.0 (d, *J* = 10.8 Hz, 2H); ESI-MS: m/z (rel.abund.%) 508 (M+, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(m-tolylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5d:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3412, 2925, 1739, 1677, 1585, 1502, 1379, 1216, 1122, 1071, 971, 750,633 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 2.20 (s, 3 H), 4.20 (s, 2 H), 4.60 (s, 2H), 5.50 (s, 2H), 5.80 (br.s, 1H),6.64-6.20 (m, 2H), 6.80 (t, *J* = 6.8 Hz, 1H), 7.40-7.10 (m, 4H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 9.0 Hz , 2H), 8.05 (d, *J* = 9.2 Hz, 2H); ESI-MS: m/z (rel.abund.%) 492 (M+), 494 (M+2).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(p-tolylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5e:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3396, 2923, 2856, 1678, 1585, 1507, 1384,1223, 1197, 1070, 979, 812,750 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 2.20 (s, 3 H), 4.20 (s, 2 H), 4.60 (s, 2H), 5.58-5.50 (m, 2H), 6.50 (br, 1H), 6.80 (d, *J* = 10.4 Hz, 2 H), 7.35-7.01 (m, 5H), 7.68 (d, *J* = 10.4 Hz, 1H), 7.80 (d, *J* = 10.8 Hz, 2H), 8.0 (d, *J* = 10.8 Hz, 2H); ESI-MS: m/z (rel.abund.%) 492 (M+), 494 (M+2).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(3-bromophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5f:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3410, 2926, 2854, 1675, 1585, 1503, 1382, 1223, 1203, 1070, 980, 814, 752, 682 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.24 (s, 2 H), 4.60 (s, 2H), 5.50 (d, *J* = 5.6 Hz, 2H), 5.80 (s, 1H), 6.68 (d, *J* = 7.78 Hz, 1H), 7.22-6.98 (m, 1H), 7.48-7.15 (m, 4H), 7.68-7.64 (m, 1 H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.88-7.84 (m, , 2H), 8.02-8.0 (m, 2H); ESI-MS: m/z (rel.abund.%) 558 (M+, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(4-bromophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5g:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3417, 3088, 2928, 2852, 1677, 1586, 1503, 1465, 1415, 1385, 1344, 1292, 1226, 1203, 1071, 971, 813, 756, 684 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.10 (s, 2 H), 4.53 (s, 2H), 5.51 (br.s, 2H), 6.12 (t, *J* = 7.2 Hz, 1H), 6.51 (br.s, 2H), 7.23-7.16 (m, 6H), 7.69 (d, *J* = 10.4 Hz, 1H), 7.80 (d, *J* = 11.2 Hz, 2H), 8.03 (d, *J* = 7.2 Hz, 2H); ESI-MS: m/z (rel.abund.%) 556 (M+), 558 (M+2, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(4-chlorophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5h:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3416, 2925, 1676, 1600, 1585, 1503, 1384, 1225, 1203, 1091, 1070, 1010, 972, 814, 757, 684 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.10 (s, 2 H), 4.52 (s, 2H), 5.50 (s, 2H), 6.55 (br.s, 1H), 7.40-7.0 (m, 7H), 7.0 (d, *J* = 10.4 Hz, 1H), 7.85 (d, *J* = 11.2 Hz, 2H), 8.05 (d, *J* = 9.6 Hz, 2H); ESI-MS: m/z (rel.abund.%) 513 (M+, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(3-fluorophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5i:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3421, 2970, 1740, 1677, 1584, 1504, 1379, 1218, 1071, 978, 813, 752,685 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.24 (s, 2 H), 4.60 (s, 2H), 5.5 (d, *J* = 5.6 Hz, 2H), 5.80 (s, 1H), 6.68 (d, *J* = 7.78 Hz, 1H), 7.22-6.96 (m, 1H), 7.48-7.15 (m, 4H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.88-7.84 (m, , 2H), 8.02-8.0 (m, 2H); ESI-MS: m/z (rel.abund.%) 496 (M+), 498 (M+2, 100).

1-(2-(4-bromophenyl)-2-oxoethyl)-4-(2-(4-fluorophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one **5j:**
Yellow syrupy liquid; Yield: 65%; IR (KBr): υ_{max} 3414, 2926, 1677, 1585, 1505, 1387, 1222, 1122, 1070, 973, 818, 760 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): δ 4.10 (s, 2 H), 4.53 (s, 2H), 5.51 (br.s, 2H), 6.12 (t, *J* = 7.2 Hz, 1H),6.51 (br.s, 2H), 7.23-7.16 (m, 6H), 7.69 (d, *J* = 10.4 Hz, 1H), 7.80 (d, *J* = 11.2 Hz, 2H), 8.03 (d, *J* = 7.2 Hz, 2H); ESI-MS: m/z (rel.abund.%) 496 (M+), 498 (M+2).

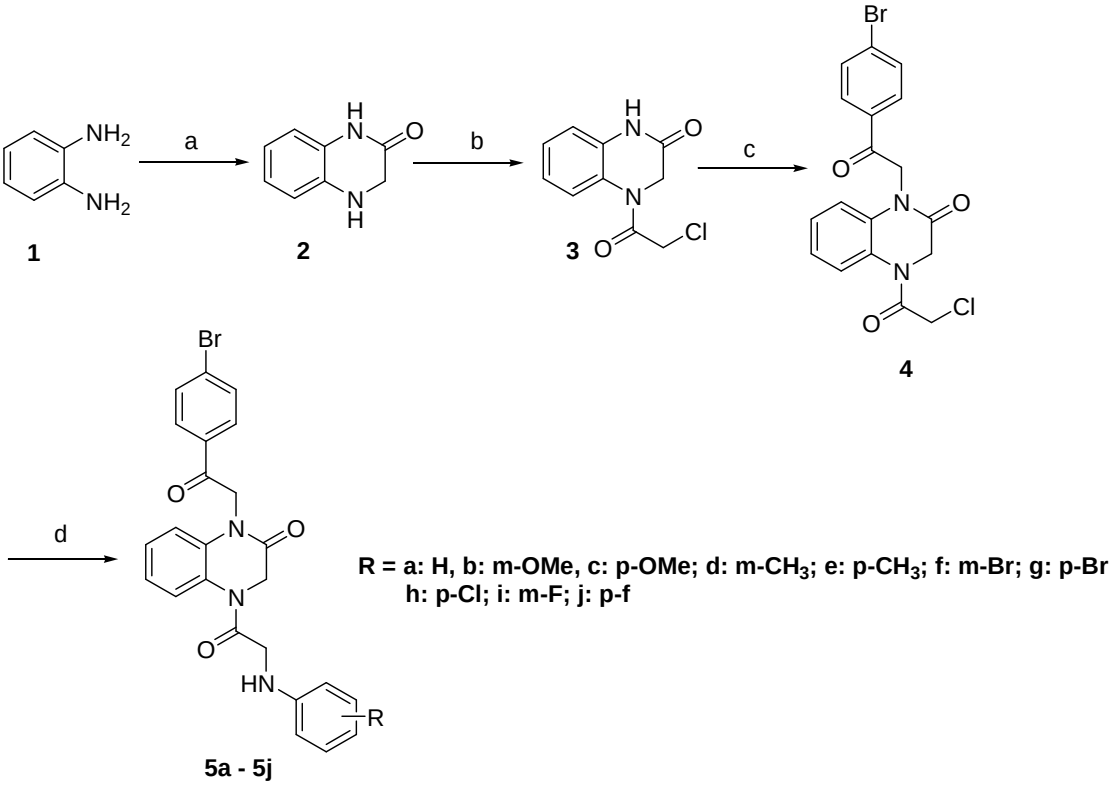
Antimicrobial Activity
The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [18]. All the compounds, **5a-5j** were screened *in-vitro* at a concentration of 100 µg/mL for antibacterial activity against two Gram-positive (Staphylococcus aureus and Staphylococcus pyogenes) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). Standard antibacterial drug ciprofloxacin (100 µg/disc) was also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **Table 1**.

RESULTS AND DISCUSSION

Synthesis of 3, 4-dihydroquinoxalin-2(1*H*)-one derivatives **5a–5j** is outlined in (**Scheme 1)**. 1,2-phenylenediamine was reacted with chloroacetic acid in water as a solvent at reflux temperature for 1 h to afford 3, 4-dihydroquinoxalin-2(1H)-one **2** in 83% yield. Compound **2** was treated with chloroacetyl chloride in DMF at room

temperature for 1 h to give compound **3** in 74 % yield. Compound **3** was reacted with 4-brom phenacyl bromide in presence of K_2CO_3 in acetonitrile at 90 ^oC to afford compound **4.** Reaction of compound **4** with various anilines in presence of $NaHCO_3$ and KI in isopropanol at reflux temperature resulted in compounds **5a-5j.**

The newly synthesized compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display good to moderate antibacterial activity against all the tested bacterial strains. From the **Table 1,** it was observed that among all the compounds tested, compound **5i** exhibited equipotent activity and **5j** showed good activity (having fluorine substituent) against all the tested bacterial strains and the remaining compounds such as compounds **5a, 5b, 5c, 5d and 5e** having methyl and methoxy substituents displayed moderate activity while the compounds **5f, 5g** and **5h** showed no activity.



Scheme-1: Experimental conditions: a) 1, Chloroacetic acid, water, reflux, 1 h; b) Chloroacetyl chloride, 2, DMF, r.t., 1 h; c) 3, 4-bromo-phenacyl bromide, K_2CO_3, ACN, 90 ^oC, 10 h; d) anilines a-j, $NaHCO_3$, KI, iso-propanol, reflux, 8-12 h.

Table 1: Antibacterial Activity of 3, 4-dihydroquinoxalin-2(1*H*)-one derivatives 5a-5j

Compound no.	R	*Gram negative bacteria*		*Gram positive bacteria*	
		E. coli	***P. aeruginosa***	***S.aureus***	***S.pyogenes***
		Zone of inhibitions			
5a	H	18	20	15	17
5b	m-OCH_3	19	18	16	15
5c	p-OCH_3	20	21	15	16
5d	m-CH_3	22	19	16	19
5e	p-CH_3	21	17	18	18
5f	m-Br	-	-	-	-
5g	p-Br	-	-	-	-
5h	p-Cl	-	-	-	-
5i	m-F	26	24	19	20
5j	p-F	28	26	21	22
Standard drug Ciprofloxacin (Conc. 100 µg /mL)	Standard drug Ciprofloxacin	28	26	21	22

'-' *means : inactive*

CONCLUSION

Novel 3,4-dihydroquinoxalin-2(1H)-one derivatives **5a – 5j** were prepared from commercially available 1,2-phenylenediamine and tested for Gram positive and Gram negative bacterial cultures. All these compounds were found to exhibit good to moderate antibacterial activity against different strains of bacteria. It was observed that among all the compounds tested, compound **5i** exhibited equipotent activity and **5j** showed good activity (having fluorine substituent) against all the tested bacterial strains and the remaining compounds such as compounds **5a, 5b, 5c, 5d and 5e** having methyl and methoxy substituent displayed moderate activity while the compounds **5f, 5g** and **5h** showed no activity

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