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Research Article

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Synthesis and Antibacterial Activity of Novel 4-Phenyl-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide Derivatives

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ABSTRACT

A series of new biologically interesting 4-phenyl-3-((quinoxalin-2-yloxy)methyl)-1,2,5-oxadiazole 2-oxide derivatives have been synthesized by 2-chloro quinoxaline and 3-(hydroxylmethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide derivatives with anhydrous potassium carbonate, potassium iodide in presence of acetone solvent under reflux condition. This method is simple, rapid-generates quinoxaline derivatives and good yield. Newly synthesized compounds were screened for their antibacterial activity against Escherichia coli, Bacillus subtilis, Pseudomonas, Staphylococcus aureus. Most of the compounds show significant antibacterial activity. The structure of quinoxaline derivatives were confirmed by using IR, ^{1}H-NMR, Mass spectroscopy.

Keywords: Glyoxalic acid; Phosphorus oxychloride; Furoxan; Potassium carbonate; Cinnamyl alcohol

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INTRODUCTION

The synthesis and chemistry of quinoxalines have attracted considerable attention in the past ten years [1,2]. Quinoxaline is commonly called 1,4-diazanaphthalene or, benzopyrazine. Melting point of quinoxaline is 29-30°C and is soluble in water. Quinoxaline molecular formula is $C_8H_6N_2$ and is formed by two aromatic rings, benzene and pyrazine. It is rare in natural state, but their synthesis is easy to perform [3]. These compounds have a wide range of applications in bacteriology, pharmacology and mycology [4-8]. Compounds containing the quinoxaline nucleus exhibit a broad spectrum of biological activity such as antitumor [9], antifungal [10], antinociceptive [11], anticonvulsant [12], antioxidant [13], antianxiety [14], antihistamic [15], antimicrobial [16], antipsychotic [17], anti-imflammatory activity [18], antispasmodic [19], antibacterial activity [16]. In addition, quinoxaline compounds possess intrinsic diuretic, uterotonic, hypertensive and phosphodiesterase inhibitor activity. They are also used in agriculture field as herbicides, fungicides and insecticides. In addition, quinoxaline derivatives are also useful information of dyes, efficient electron luminescent materials, organic semiconductor, cavitands and dehydroannulenes [20-22]. The wide range of biological activity of compounds containing a furoxan (1,2,5-oxadiazole-N-oxide) or benzofuroxan heterocycle has been known for decades [23-25]. This is a heterocycle of the isoxazole family and an amine oxide derivative of furazan. In recent years, the furoxan moiety has been the subject of increased attention, pioneered by Gasco and others, owing to a plethora of interesting biological activities observed against a diverse range of targets [26-32]. We now designed and synthesized a series of novel quinoxaline derivatives from quinoxalin-2-ol [33-35] and derivatives of 3-(chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide with anhydrous K_2CO_3 in presence of acetone solvent.

EXPERIMENTAL SECTION

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (m.p.) determinations were performed by using Mel-temp apparatus and are uncorrected. H-NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as, s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap mass spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR spectrometer.

3-(Hydroxymethyl)-4-Phenyl-1,2,5-Oxadiazole 2-Oxide (5)
To a stirred solution of $NaNO_2$ (3 g, 72 mmol) in water (50 mL) was added dropwise cinnamyl alcohol (2 g, 15 mmol) in HOAc (5 mL). The reaction mixture was stirred at room temperature for 4 h and then neutralized with $NaHCO_3$, followed by the extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue obtained on column purification (silica, petroleum ether / EtOAc, 7:1 as eluent) afforded the furoxan alcohol (0.86 g, 30%).

3-(Chloromethyl)-4-Phenyl-1,2,5-Oxadiazole 2-Oxide (6)
To a stirred solution of 5 (192 mg, 1mmol) and pyridine (0.35 mL, 4 mmol) in anhydrous CH_2Cl_2 (15 mL) was added $SOCl_2$ (0.5 mL) in ice-bath. The mixture was stirred at room temperature for 3 h and then washed with ice water, saturated $NaHCO_3$ solution, and brine successively. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give clear oil.

General Procedure for the Preparation of 7 (a-j)
3-(chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (1mmol) (6) and quinoxaline-2-ol[34] (1mmol) (2) in acetone (10 mL) was added anhydrous K_2CO_3 (1.5 mmol). After refluxing for 5 h, the reaction mixture was concentrated in vacuo. Water (10 mL) was then added to the residue, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue obtained on column purification (silica, elution with 20% EtOAc in hexane) and dried to obtain products of 7 (a-i).

4-Phenyl-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7a):
^{1}H NMR (400 MHz, $CDCl_3$): 8.51 ppm (s, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 7.61 (t, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 5.16 (s, 2H, CH_2), 7.68 (d, 1H, Ar-H), 7.53 (t, 1H, Ar-H), 7.39 (t, 1H, Ar-H), 7.52 (t, 1H, Ar-H), 7.75 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.9 ppm, 129.4, 128.1, 129.0, 138.7, 136.5, 176.8, 137.4, 71.8, 142.1, 144.7, 139.2, 128.4, 130.1, 129.6, 130.4, 128.1. LC-MS m/z, 321.16 $[M+H]^+$.

4-(4-Fluorophenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7b):
^{1}H NMR (400 MHz, $CDCl_3$): 8.49 ppm (s, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 5.09 (s, 2H, CH_2), 8.19 (d, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 8.16 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.3 ppm, 129.3, 128.1, 129.0, 138.7, 136.5, 176.8, 137.6, 71.3, 141.9, 144.9, 129.5, 131.2, 116.8, 173.1, 116.3, 131.1; LC-MS m/z, 339.19 $[M+H]^+$.

4-(4-Chlorophenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7c):
^{1}H NMR (400 MHz, $CDCl_3$): 8.55 ppm (s, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.82 (d, 1H, Ar-H), 5.32 (s, 2H, CH_2), 7.93 (d, 1H, Ar-H), 7.62 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.96 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.5 ppm, 129.7, 127.9, 129.4, 138.7, 136.8, 176.9, 137.1, 73.1, 142.3, 145.1, 131.5, 127.2, 133.5, 139.5, 132.7, 128.3; LC-MS m/z, 355.37 $[M+H]^+$.

4-(4-Bromophenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7d):
^{1}H NMR (400 MHz, $CDCl_3$): 8.53 ppm (s, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.67 (t, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 5.35 (s, 2H, CH_2), 7.75 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.3 ppm, 129.5, 128.1, 129.0, 138.2, 136.9, 176.8, 134.5, 73.0, 143.2, 145.3, 130.6, 128.7, 135.4, 124.3, 134.3, 129.1; LC-MS m/z, 400.09 $[M+H]^+$.

3-((Quinoxalin-2-yloxy)Methyl)-4-(p-tolyl)-1,2,5-Oxadiazole 2-Oxide (7e):
^{1}H NMR (400 MHz, $CDCl_3$): 8.71 ppm (s, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 5.47 (s, 2H, CH_2), 7.63 (d, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 2.90 (s, 3H, CH_3), 7.32 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 129.2 ppm, 131.6, 128.3, 130.4, 141.4, 138.7, 181.5, 139.7, 75.0, 143.6, 147.8, 131.8, 126.4, 129.7, 21.0, 139.4, 130.6, 126.8; LC-MS m/z, 335.27 $[M+H]^+$.

4-(4-Methoxyphenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7f):
^{1}H NMR (400 MHz, $CDCl_3$): 8.92 ppm (s, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 5.45 (s, 2H, CH_2), 7.62 (d, 1H, Ar-H), 7.21 (d, 1H, Ar-H), 4.73 (s, 3H, CH_3), 7.23 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.7 ppm, 129.3, 128.7, 129.0, 138.7, 136.5, 176.8, 137.9, 73.9, 143.2, 145.6, 124.9, 127.3, 119.2, 168.1, 61.3, 120.3, 126.9; LC-MS m/z, 351.17 $[M+H]^+$.

4-(4-Nitrophenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7g):
^{1}H NMR (400 MHz, $CDCl_3$): 8.68 ppm (s, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 5.63 (s, 2H, CH_2), 8.21 (d, 1H, Ar-H), 8.67 (d, 1H, Ar-H), 8.64 (d, 1H, Ar-H), 8.25 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 129.6 ppm, 131.6, 128.7, 129.4, 138.7, 136.5, 176.8, 138.4, 75.0, 144.7, 146.5, 140.2, 128.9, 126.3, 151.7, 126.9, 129.2; LC-MS m/z, 366.24 $[M+H]^+$.

4-(4-(Dimethylamino)Phenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7h):
^{1}H NMR (400 MHz, $CDCl_3$): 8.73 ppm (s, 1H, Ar-H), 7.84 (d, 1H, Ar-H), 7.57 (t, 1H, Ar-H), 7.59 (t, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 5.71 (s, 2H, CH_2), 7.54 (d, 1H, Ar-H), 7.04 (d, 1H, Ar-H), 4.76 (s, 3H, CH_3), 4.76 (s, 3H, CH_3), 7.06 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 128.9 ppm, 129.3, 127.8, 129.3, 140.7, 138.5, 179.4, 139.6, 77.2, 144.9, 147.2, 129.5, 131.5, 116.4, 165.5, 52.5, 52.5,116.7, 131.9; LC-MS m/z, 364.32 $[M+H]^+$.

4-(4-(Diethylamino)phenyl)-3-((Quinoxalin-2-yloxy)Methyl)-1,2,5-Oxadiazole 2-Oxide (7i):
^{1}H NMR (400 MHz, $CDCl_3$): 8.72 ppm (s, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.56 (t, 1H, Ar-H), 7.53 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 5.45 (s, 2H, CH_2), 7.59 (d, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 4.24 (q, 2H, CH_2), 4.24 (q, 2H, CH_2), 2.1 (t, 1H, CH_3), 2.1 (t, 1H, CH_3), 7.05 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H); ^{13}C NMR (400 MHz): 129.8, 131.2, 128.4, 129.2, 140.6, 138.4, 184.2, 139.0, 75.0, 146.3, 148.2, 122.7, 129.6, 119.4, 153.7, 119.7, 129.5, 51.2, 51.5, 19.5, 19.5; LC-MS m/z, 392.09 $[M+H]^+$.

RESULTS AND DISCUSSION

O-Phenylene di amine (1) was treated with glyoxalic acid (50% H_2O) in presence of methanol at 0°C to obtain previously reported quinoxaline-2-ol [33-35] (2). Now cinnamaldehyde (3) was treated with sodium borohydride in presence of methanol at 0°C after completion of addition, stirred at roomtemperature for 2 h to form cinnamyl alcohol (4). To a stirred solution of sodium nitrite in water was added dropwise cinnamyl alcohol in acetic acid and stirred at room temperature for 4 h to obtain previously reported 3-(hydroxymethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide [36] (furoxan alcohol) (5). To a stirred solution of (5) and pyridine in anhydrous dichloromethane was added thionyl chloride in an ice bath. The reaction mixture was stirred at room temperature for 3h followed by simple processing resulted in the formation of already reported 3-(chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide [37] (6). To a solution of the crude oil (6) and quinoxaline-2-ol (2) in acetone was added anhydrous K_2CO_3 and maintain reflux condition for 5 h, followed by simple processing resulted in the formation to 4-phenyl-3-(quinoxalin-2-yloxy)-1,2,5-oxadiazole 2-oxide (7). This authentic condition has been found to be a general one and has been extended to different types of furoxan alcohols such as 4-(4-fluorophenyl)-3-(hydroxymethyl)-1,2,5-oxadiazole 2-oxide, 4-(4-chlorophenyl)-3-(hydroxymethyl)-1,2,5-oxadiazole 2-oxide, 4-(4-bromophenyl)-3-(hydroxymethyl)-1,2,5-oxadiazole 2-oxide, 3-(hydroxymethyl)-4-(p-tolyl)-1,2,5-oxadiazole 2-oxide, 3-(hydroxymethyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole 2-oxide, 3-(hydroxymethyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole 2-oxide, 4-(4-dimethylamino) phenyl)-3-(hydroxymethyl)-1,2,5-oxadiazole 2-oxide, 4-(4-(diethylamino)phenyl)-3-(hydrox ylmethyl)-1,2,5-oxadiazole 2-oxide (Figure 1 and Table 1).

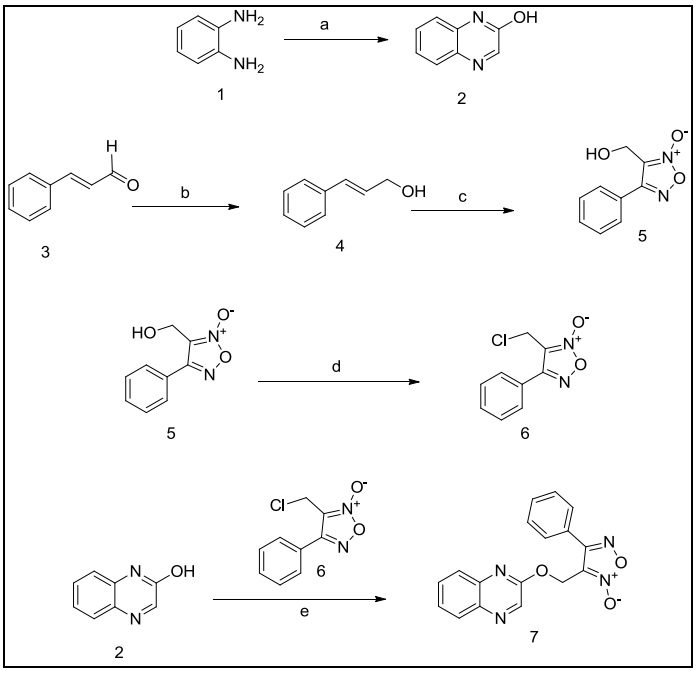
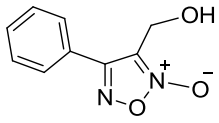
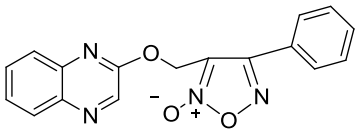
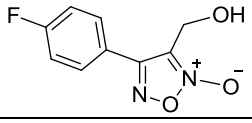
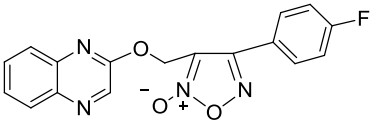
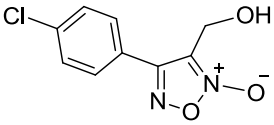
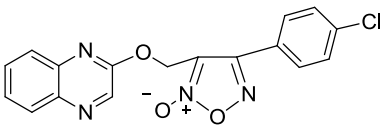
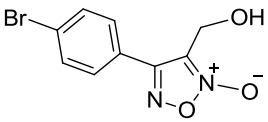
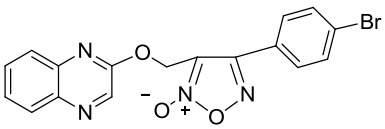
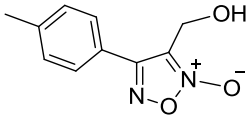
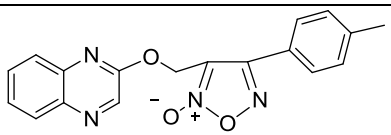
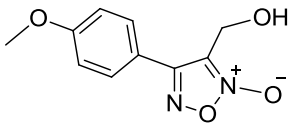
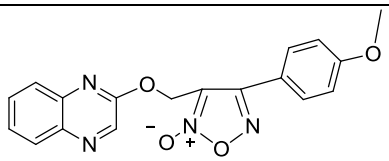
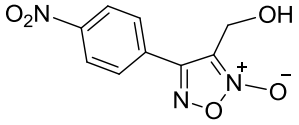
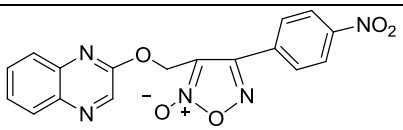
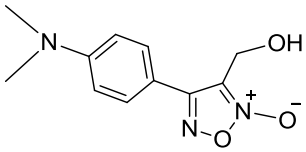
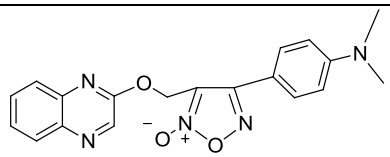
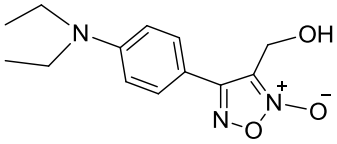
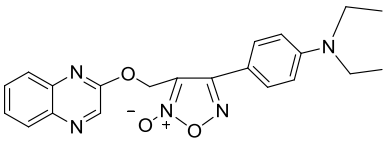


Figure 1: Reagents and Conditions: a: glyoxalic acid, methanol, at 0°C for 2 hr; b: sodium borohydride, methanol, RT 3 hr; c: sodium nitrite, acetic acid, RT, 4 hr; d: thionyl chloride, dichloromethane, pyridine, RT, 3 hr; e: potassium carbonate, potassium iodide, acetone, reflux condition in 5 hr

Table 1: Quinoxaline-2-ol react with derivatives of 3-(hydroxymethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide in presence of K_2CO_3 under reflux condition in aceton solvent system

S.no.	Starting material	Reacent	Product	T / h	Yield
1	2			5 h	82%
2	2			5 h	80%
3	2			5 h	80%
4	2			5 h	85%
5	2			6 h	73%

6	2			6 h	70%
7	2			6 h	71%
8	2			6 h	78%
9	2			6 h	83%

Biological Activity

Newly synthesized compounds were screened for antibacterial activity study purpose micro-organisms employed were Gram positive (*Bacillus substillis, Streptococcus aureus*), Gram negative (*E. coli, Pseudomonas vulgaris*) (Table 2).

Table 2: Antibacterial activity (Diameters in mm of zone of inhibition)

S.No.	Product	*E. coli (mm)*	*Bacillus (mm)*	*S. aureus (mm)*	*Psedomonas (mm)*
1	7a	18	17	15	11
2	7b	22	18	12	10
3	7c	17	15	18	13
4	7d	12	14	14	10
5	7e	18	17	17	16
6	7f	14	11	14	13
7	7g	28	19	26	22
8	7h	22	18	16	18
9	7i	24	20	23	19

CONCLUSION

In this study, we synthesized and characterized a series of novel quinoxaline derivatives. The title compounds were confirmed by 1 H-NMR, IR, and Mass spectral analysis and these analogues generated good anti-bacterial activity.

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