SENRA Academic Publishers, Burnaby, British Columbia
Vol. 3, No. 3, pp. 983-992, 2009
ISSN: 1715-9997

Canadian Journal of pure&applied sciences

SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF PHENYL AND FURAN-2-YL[1,2,4] TRIAZOLO[4,3-a]QUINOXALIN-4(5*H*)-ONE AND THEIR HYDRAZONE PRECURSORS

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ABSTRACT

A variety of 1-(s-phenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one **(3a-3h)** and 1-(s-furan-2-yl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one **(5a-d)** were synthesized from thermal annelation of corresponding hydrazones **(2a-h)** and **(4a-d)** respectively in the presence of ethylene glycol which is a high boiling solvent. The structures of the compounds prepared were confirmed by analytical and spectral data. Also, the newly synthesized compounds were evaluated for possible antimicrobial activity. 3-(2-(4-hydroxylbenzylidene)hydrazinyl)quinoxalin-2(1*H*)-one **(2e)** was the most active antibacterial agent while 1-(5-Chlorofuran-2-yl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one **(5c)** stood out as the most potent antifungal agent.

Keywords: 3-Hydrazinoquinoxalin-2(1*H*)-one, benzodiazine, antifungal agent, uv-visible, spectroscopy, benzaldehyde.

INTRODUCTION

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. In the recent years, there has been considerable attention on the preparation of useful heterocyclic compounds in organic synthesis. The motivation for this present study was the known widespread application of benzo-fused N-heterocycles, especially quinoxalines (Alleca *et al.,* 2003) which was reported to have anti-cancer (Solano *et al*., 2007; Zarranz *et al*., 2004), anti-inflammatory (Olayiwola *et al*., 2007) anti-malarial (Zarranz *et al*., 2005), antimycobacterial (Seitz *et al*., 2002) activities, among others.

Quinoxaline belongs to the family of benzodiazine with its nitrogen heteroatoms situated at 1 and 4-positions. The most common way to construct quinoxaline ring is by simple condensation reaction between ortho-phenylenediamine and oxalic acid or its derivatives. In a nutshell, quinoxalines are relatively easy to prepare and various derivatives have been synthesized (Obafemi and Akinpelu, 2005; Refaat *et al*., 2004; Kim and Kim, 2003; Nasr *et al*., 2002; Ali *et al.,* 2000) in order to obtain biologically active materials (Heravi *et al.,* 2007; Stasweszka *et al*., 2005). Quinoxaline nucleus is a common substructure of many biologically (Catarzi *et al*., 2008; El-Hawash *et al*., 2006) and pharmacologically (Colotta *et al*., 2008; Catarzi *et al*., 2005; Holschbach *et al*., 2005) active compounds. Furthermore, quinoxaline moiety is found as the skeletal structure in various antibiotics such as echinomycin (Hasaninejad *et al*., 2008), levomycin (Ammar *et al*., 2009) and actinoleutin (Islami *et al*., 2008; Aggarwal *et al*., 2006) that are known to inhibit growth of gram-positive bacteria and are active against various transplantable tumors. Quinoxalines are useful precursors for the synthesis of some fused ring derivatives such as thieno- (Zaleska *et al.,* 2001), pyrrolo (Kollenz *et al*., 2001), pyrimido (Charushin *et al*., 2001) and more especially, triazoloquinoxaline.

Triazoloquinoxaline and their hydrazones derivatives are classes of heterocycles that are of considerable interest because of the diverse range of their biological properties. Therefore, large efforts have been directed towards the synthetic manipulation of quinoxaline derivatives in order to discover more useful compounds. For instance, a number of methods have been developed for the synthesis of substituted quinoxalines (Kumar *et al*., 2008; Vicente *et al*., 2008; Zhenjiang *et al*., 2008; Harrak *et al*., 2007; Hazarika *et al.,* 2007; Szekelyhidi *et al.,* 2005; Vidaillac *et al*., 2005) as well as hydrazone frameworks (Sridharan *et al*., 2007; Abd-Elhafez *et al*., 2003; Vicini *et al*., 2003). However, incorporation of hydrazone into quinoxaline and subsequent generation of triazolo moieties may lead to increase in potency of such library.

Multi-drug resistance is one of the major immediate threats to human health today (Masunari and Tavares, 2007; Kaatz *et al*., 2005; Dyatkina *et al*., 2002). Also,

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epidemiological studies have also revealed that emergence of new diseases is at the alarming rates in the recent time (Nayak *et al*., 2007). Based on the various challenges aforementioned among others, there is a continuous need for the synthesis of new organic compounds as potential antimicrobial agents. Thus, it is conceivable in this present work, to develop a series of hydrazinylquinoxalines and triazoloquinoxalines with the aim of investigating its antimicrobial properties.

MATERIALS AND METHODS

Chemistry

Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. Infra red spectra were recorded as KBr pellets on a Buck Spectrometer while uv-visible spectra were recorded on a Heλioseα ν2.02 Unicam Spectrophotometer using methanol solvent. ^{1}H- and ^{13}C-NMR were run on a Bruker-AC 400-MHz and JEOL-JNM-GX 50-MHz spectrometer (δ in ppm relative to Me_4Si) respectively using deuteriated methanol. Mass spectra were run on Finnigan MAT 312 machine. All compounds were routinely checked by TLC on silical gel G plates using $CHCl_3$:CH_3OH (9:1, v/v) solvent system and the developed plates were visualized by UV light. The elemental analysis (C, H, N) of compounds were performed using a Carlo Erba-1108 elemental analyzer. Solvents used were of analytical grade and, when necessary, were purified and dried by standard methods. All furfural derivatives, orthophenylenediamine, ethanol and ethylene glycol were obtained from Aldrich Chemical, Germany while benzaldehyde derivatives as well as hydrazine hydrate and oxalic acid dihydrate were obtained from BDH Chemical Limited. Other solvents were obtained from May and Baker Limited.

Synthesis of 3-Hydrazinoquinoxalin-2(1*H*)-one (1). To a solution of pure 1,2,3,4-tetrahydroquinoxaline-2,3-dione (20.1 g, 124.0 mmol) in hydrazine hydrate (100.0 ml, 2.2 mol), was added water (50 mL) drop wise with constant stirring at 100^{o}C. The resulting mixture was refluxed under continuous stirring for 3h. The mixture was allowed to cool and the formed precipitate was filtered, recrystallized from ethanol to give **1.** ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 5.81(s-br, 2H, NH_2; D_2O exchangeable), 7.49-7.96(m, 4H, Ar-H), 8.14(s, 1H, NH; D_2O exchangeable), 12.55(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 190.5(C=O), 141.9, 134.2, 125.7, 119.6, 117.0, 115.4, 110.4 ppm. IR (KBr, cm^{-1}): ν_{max} 3412(N-H), 3280(N-H), 3175(N-H), 1679(C=O), 1620(C=C). λ_{max} in nm (log ε_{max}): 216(4.34), 247(3.75s), 327(3.61s). MS: in m/z[rel. %]: 176[M^{+}, 55.5 %], 161[92.3 %], 146[85.5 %], 118[100 %], 106[80.1 %].

General procedure for synthesis of 3-(2-s-benzylidene)hydrazinyl)quinoxalin-2(1*H*)-one (2a-h). To a ground mixture of 3-hydrazinoquinoxalin-2(1*H*)-one **1** (1.0g, 5.7 mmol) and corresponding benzaldehyde (5.7 mmol), was added ethanol (20mL) with a continuous stirring until homogeneity was achieved. The resulting mixture was refluxed at a controlled temperature of 95^{o}C for 3h. The solution was allowed to cool and the formed precipitate was filtered, recrystallized from ethanol to give **(2a-h)**.

Synthesis of 3-(2-benzylidene)hydrazinyl)quinoxalin-2(1*H*)-one (2a). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.01 (s, 1H, NH; D_2O exchangeable), 5.35 (s, 1H, OH; D_2O exchangeable), 6.85-7.78 (m, 4H, Ar-H), 7.09-8.27(m, 4H, Q-Ar), 8.00 (s, 1H, NH; D_2O exchangeable), 8.54 (s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 160.8(C=O), 158.0(C-OH), 157.6, 146.8(N=CH), 142.7, 131.7, 130.6, 130.6, 129.1, 126.3, 125.9, 123.5, 116.0, 116.0, 115.2 ppm. IR (KBr, cm^{-1}): ν_{max} 3241(N-H), 1685(C=O), 1612(C=C), 1563(C=N). λ_{max} in nm (log ε_{max}): 212(4.58), 276(4.03), 308(4.02s), 352(4.48), 376(4.60), 394(3.84s).

Synthesis of 3-(2-(2-nitrobenzylidene)hydrazinyl) quinoxalin-2(1*H*)-one (2b). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.03 (s, 1H, NH; D_2O exchangeable), 7.09-8.29 (m, 4H, Q-Ar), 7.59-8.09(m, 4H, Ar-H), 8.00 (s, 1H, NH; D_2O exchangeable), 8.54(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.5, 147.8, 143.3, 142.7, 134.9, 131.9, 131.7, 130.1, 129.1, 128.4, 125.9, 124.0, 123.5, 115.3 ppm. IR (KBr, cm^{-1}): ν_{max} 1685 (C=O), 1606(C=C), 1563(C=N), 979(NO_2). λ_{max} in nm (log ε_{max}): 220(4.29), 328(3.72), 368(3.97), 383(3.94).

Synthesis of 3-(2-(2-chlorobenzylidene)hydrazinyl) quinoxalin-2(1*H*)-one (2c). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.01(s, 1H, NH; D_2O exchangeable), 7.09-8.28(m, 4H, Q-Ar), 7.40-7.77(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.99(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 142.7, 138.7, 134.7, 133.9, 132.4, 131.7, 130.1, 129.1, 127.2, 126.9, 125.9, 123.5, 115.2 ppm. IR (KBr, cm^{-1}): ν_{max} 3214(N-H), 1685(C=O), 1606(C=C), 1565(C=N). λ_{max} in nm (log ε_{max}): 216(3.85), 372(3.56).

Synthesis of 3-(2-(4-(N,N-dimethylaminobenzylidene) hydrazinyl)quinoxalin-2(1*H*)-one (2d). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.02(s, 1H, NH; D_2O exchangeable), 3.06(s, 6H, *J* = 7Hz, 2x CH_3), 6.81-7.50(m, 4H, Ar-H), 7.07-8.25(m, 4H, ArH), 8.00 (s, 1H, NH; D_2O exchangeable), 8.52(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 153.4, 146.8, 142.7, 131.7, 129.1, 128.3, 128.3, 125.9, 123.5, 123.2, 111.9, 111.9, 115.2, 41.6, 41.6(-N(CH_3)$_2$) ppm. IR (KBr, cm^{-1}): ν_{max} 3351(N-H), 2925(CH aliphatic), 1685(C=O), 1606(C=C), 1563(C=N). λ_{max} in nm (log ε_{max}): 224 (4.71), 332 (4.50), 396(4.81).

Synthesis of 3-(2-(4-hydroxylbenzylidene) hydrazinyl) quinoxalin-2(1*H*)-one (2e). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 5.35(s, 1H, OH; D_2O exchangeable), 6.85-7.78(m, 4H, Ar-H), 7.00(s, 1H, NH; D_2O exchangeable), 7.09-8.27(m, 4H, Q-Ar), 8.00(s, 1H, NH; D_2O exchangeable), 8.54(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 160.8(C-OH), 158.0(C=O), 157.6, 146.8(N=CH), 142.7, 131.7, 130.6, 130.6, 129.1, 126.3, 125.9, 123.5, 116.0, 116.0, 115.2 ppm. IR (KBr, cm^{-1}): ν_{max} 3241(N-H), 1685(C=O), 1612(C=C), 1563(C=N). λ_{max} in nm (log ε_{max}): 212(4.58), 276(4.03), 308(4.02s), 352(4.48), 376 (4.60), 394 (5.84s). MS: in m/z[rel. %]: 280 [M^+, 47 %], 263[M-OH, 79 %], 187[88 %], 118[100 %].

Synthesis of 3-(2-(4-hydroxyl-3-methoxybenzylidene) hydrazinyl)quinoxalin-2(1*H*)-one (2f). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.01(s, 1H, NH; D_2O exchangeable), 3.83(s, 3H, *J* = 8.5Hz, OCH_3), 5.35(s, 1H, OH; D_2O exchangeable), 6.91-7.52(m, 3H, Ar-H), 7.09-8.27(m, 4H, Q-Ar), 8.00(s, 1H, NH; D_2O exchangeable), 8.36(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 151.0(C-OH), 149.3, 146.8, 142.7, 131.7, 130.9, 129.1, 125.9, 123.5, 122.9, 117.0, 115.2, 112.1, 56.1(OCH_3) ppm. IR (KBr, cm^{-1}): ν_{max} 3241(N-H), 1685(C=O), 1620(C=C), 1510(C=N), 1278(C-O). λ_{max} in nm (log ε_{max}): 220(4.32), 348(3.37), 376(3.42).

Synthesis of 3-(2-(3-hydroxylbenzylidene)hydrazinyl) quinoxalin-2(1*H*)-one (2g). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.01(s, 1H, NH; D_2O exchangeable), 5.35(s, 1H, OH; D_2O exchangeable), 7.02-7.46(m, 4H, Ar-H), 7.09-8.28(m, 4H, Q-Ar), 8.00(s, 1H, NH; D_2O exchangeable), 8.36(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.6(C-OH), 158.0(C=O), 157.6, 146.8, 142.7, 138.7, 131.7, 130.2, 129.1, 125.9, 123.5, 121.8, 118.2, 115.2, 114.9 ppm. IR (KBr, cm^{-1}): ν_{max} 3240(N-H), 1685(C=O), 1612(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 220(4.13), 368(4.19), 388(3.89).

Synthesis of 3-(2-(2-hydroxylbenzylidene)hydrazinyl) quinoxalin-2(1*H*)-one (2h). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.01(s, 1H, NH; D_2O exchangeable), 5.35(s, 1H, OH; D_2O exchangeable), 7.01-7.66(m, 4H, Ar-H), 7.09-8.27(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.78(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 157.2(C-OH), 146.0, 142.7, 132.4, 131.7, 129.1, 127.5, 125.9, 123.5, 121.4, 118.5, 117.8, 115.2 ppm. IR (KBr, cm^{-1}): ν_{max} 3240(N-H), 1686(C=O), 1618(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 212(3.68), 356(3.46), 372(3.51), 392(3.40).

General procedure for the synthesis of 1-(s-phenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3a-3h). To a dried pure corresponding hydrazone **2** (10mmol) was added ethylene glycol (5 mL) and the reacting mixture was heated at 200^{o}C under reflux for 5 h. The solution was allowed to stand at room temperature after which it was poured into crushed ice (5g). The product was filtered off, dried and crystallized from ethanol.

Synthesis of 1-phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3a). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.32-7.81(m, 4H, Ar-H), 7.41-8.28(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 144.9, 137.2, 134.4, 132.6, 131.1, 129.2, 129.2, 129.2, 127.5, 127.5, 127.3, 126.6 ppm. IR (KBr, cm^{-1}): ν_{max} 1685(C=O), 1610(C=C), 1560(C=N). λ_{max} in nm (log ε_{max}): 216(3.67), 360(4.00), 389(3.62).

Synthesis of 1-(2-nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3b). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.30-7.81(m, 4H, Q-Ar-H), 7.67-8.05(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 150.1, 144.9, 137.2, 135.3, 133.0, 132.6, 129.6, 129.2, 127.3, 126.6, 126.2, 124.4 ppm. IR (KBr, cm^{-1}): ν_{max} 1685(C=O), 1605(C=C), 1565(C=N), 979(NO_2). λ_{max} in nm (log ε_{max}): 220(3.69), 325(3.98), 361(3.47). MS: in m/z[rel. %]: 307[M^+, 61 %], 261[M^+- NO_2, 82 %], 185[91 %], 118[100 %].

Synthesis of 1-(2-chlorophenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3c). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.30-7.82(m, 4H, Q-Ar-H), 7.36-7.73(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 144.9, 138.5, 137.2, 132.6, 132.2, 130.1, 129.3, 129.2, 128.9, 127.3, 127.3, 126.6 ppm. IR (KBr, cm^{-1}): ν_{max} 3214(N-H), 1685(C=O), 1606(C=C), 1560(C=N). λ_{max} in nm (log ε_{max}): 216(4.19), 374(3.91).

Synthesis of 1-(4-(N,N-dimethylamino)phenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3d). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 3.06(s, 6H, *J* = 7.1Hz, 2x CH_3), 6.82(dd, 2H, *J* = 3, 10Hz, Ar-H), 7.97(dd, 2H, *J* = 3.5, 11Hz, Ar-H), 7.37-7.86(m, 4H, Q-Ar-H), 8.02(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 155.3, 144.9, 137.2, 132.6, 129.2, 128.4, 128.4, 127.3, 126.6, 123.9, 112.7, 112.7, 41.3, 41.3 ppm. IR (KBr, cm^{-1}): ν_{max} 2925 (CH aliphatic), 1685(C=O), 1606(C=C), 1563(C=N). λ_{max} in nm(log ε_{max}):220(3.82), 345(3.44).

Synthesis of 1-(4-hydroxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3e). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 5.34(s, 1H, OH; D_2O exchangeable), 6.86(dd, 2H, *J* = 3, 10Hz, Ar-H), 7.32-7.83(m, 4H, Q-Ar-H), 7.91(dd, 2H, *J* = 3.6, 11.2Hz, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2 (C=O), 162.3, 158.9, 158.5 (C-OH), 144.9, 137.2, 132.6, 130.7, 130.7, 129.2, 127.3, 127.0, 126.6, 116.7, 116.7 ppm. IR (KBr, cm^{-1}): ν_{max} 3239(N-H), 1685 (C=O),

1612(C=C), 1563(C=N). λ_{max} in nm (log ε_{max}): 212(4.38), 276(4.07), 352(4.48), 379(4.32).

Synthesis of 1-(4-hydroxyl-3-methoxyphenyl)-[1,2,4] triazolo[4,3-a]quinoxalin-4(5*H*)-one (3f). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 3.83(s, 3H, OCH_3), 5.35(s, 1H, OH; D_2O exchangeable), 6.90-7.48(m, 3H, Ar-H), 7.35-7.85(m, 4H, Ar-H), 8.01(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 162.3, 158.9, 155.3, 148.7(C-OH), 148.0, 144.9, 137.2, 132.6, 129.2, 127.3, 126.6, 124.2, 123.0, 115.8, 112.7, 51.6 ppm. IR (KBr, cm^{-1}): ν_{max} 3161(N-H), 1685(C=O), 1615 (C=C), 1514(C=N), 1278(C-O). λ_{max} in nm (log ε_{max}): 220(3.75), 348(3.99), 371(3.55).

Synthesis of 1-(3-hydroxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3g). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 5.35(s, 1H, OH; D_2O exchangeable), 6.91-7.84(m, 4H, Ar-H), 7.30-7.84(m, 4H, Q-Ar), 8.01(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 157.5(C-OH), 144.9, 137.2, 132.6, 132.0, 130.6, 129.2, 127.3, 126.6, 120.1, 115.9, 112.9 ppm. IR (KBr, cm^{-1}): ν_{max} 3240(N-H), 1685(C=O), 1620(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 220 (3.84), 350(3.41), 379(3.33).

Synthesis of 1-(2-hydroxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (3h). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 5.35(s, 1H, OH; D_2O exchangeable), 7.01-7.63(m, 4H, Ar-H), 7.32-7.82(m, 4H, Q-Ar-H), 8.00 (s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 162.3, 158.9, 154.1(C-OH), 144.9, 137.2, 132.6, 131.9, 130.1, 129.2, 127.3, 126.6, 121.8, 118.3, 117.8 ppm. IR (KBr, cm^{-1}): ν_{max} 3240(N-H), 1687(C=O), 1616(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 215(4.29), 354(3.81), 395(4.02).

General procedure for the synthesis of 3-(2-(s-furan-2-yl)methylene)hydrazinyl)quinoxalin-2(1*H*)-one (4a-4d). To a homogeneous mixture of 3-hydrazino-quinoxalin-2(1*H*)-one **1** (1.0 g, 5.7 mmol) and corresponding furfural (5.7 mmol), was added ethanol (20 mL) with a continuous stirring until homogeneity was achieved. The resulting mixture was refluxed at a controlled temperature of 95^{o}C for 4h. The solution was allowed to cool and the formed precipitate was filtered, recrystallized from ethanol to give **(4a-4d)**.

3-(2-(furan-2-yl)methylidene)hydrazinyl)quinoxalin-2(1*H*)-one (4a). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 6.52-7.75(m, 3H, Fr-H), 7.00 (s, 1H, NH; D_2O exchangeable), 7.09-8.28(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.45(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 149.1, 144.4, 142.7, 134.6(N=CH), 131.7, 129.1, 125.9, 123.6, 118.9, 115.2, 112.6 ppm. IR (KBr, cm^{-1}): ν_{max} 3140(N-H), 1690(C=O), 1620(C=C). λ_{max} in nm (log ε_{max}): 220 (4.02), 265(4.13), 310(3.95).

3-(2-(5-nitrofuran-2-yl)methylidene)hydrazinyl) quinoxalin-2(1*H*)-one (4b). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.00(s, 1H, NH; D_2O exchangeable), 7.09-7.59(dd, 2H, *J* = 2.5, 8.5Hz, Fr-H), 7.09-8.27(m, 4H, Ar-H), 8.01(s, 1H, NH; D_2O exchangeable), 8.45(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 152.0, 151.8, 142.7, 134.7(N=CH), 131.7, 129.1, 125.9, 123.5, 115.2, 114.4, 114.3 ppm. IR (KBr, cm^{-1}): ν_{max} 3140(N-H), 1685(C=O), 1612(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 220(4.02), 244(4.11), 270(3.93), 290 (3.84).

3-(2-(5-chlorofuran-2-yl)methylidene)hydrazinyl) quinoxalin-2(1*H*)-one (4c). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 6.54(s, 2H, Fr-H), 7.00(s, 1H, NH; D_2O exchangeable), 7.09-8.27(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.45(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 149.5, 142.7, 134.6(N=CH), 133.4, 131.7, 129.1, 125.9, 123.5, 115.2, 112.5, 107.1 ppm. IR (KBr, cm^{-1}): ν_{max} 3140(N-H), 1685(C=O), 1618(C=C), 1575(C=N). λ_{max} in nm (log ε_{max}): 220(3.99), 273(3.72), 305(3.61).

3-(2-(5-methylfuran-2-yl)methylidene)hydrazinyl) quinoxalin-2(1*H*)-one (4d). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 2.30(s, 3H, *J* = 8Hz -CH_3), 6.08-6.85(dd, 2H, *J* = 3.5, 9.2Hz, Fr-H), 7.00 (s, 1H, NH; D_2O exchangeable), 7.09-8.27(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.45(s, 1H, N=CH). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 158.0(C=O), 157.6, 155.6, 147.3, 142.7, 134.6(N=CH), 131.7, 129.1, 125.9, 123.5, 115.2, 110.1, 106.7, 13.4(CH_3). IR (KBr, cm^{-1}): ν_{max} 3412 (N-H), 2929(CH aliphatic), 1706(C=O), 1606(C=C), 1515(C=N), 1266(C-O furan). λ_{max} in nm (log ε_{max}): 220(4.01), 274(3.79), 310(3.66), 325(4.11).

General procedure for the synthesis of 1-(5-s-furan-2-yl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (5a-5d). To a dried pure corresponding hydrazone **4** (10mmol) was added ethylene glycol (5 mL) and the reacting mixture was heated at 200^{o}C under reflux for 7 h. The solution was allowed to stand at room temperature after which it was poured into crushed ice (5g). The product was filtered off, dried and crystallized from ethanol.

1-(Furan-2-yl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (5a). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 6.68(t, 1H, *J* = 7.5Hz, Fr-H), 7.21(d, 1H, *J* = 7.5Hz Fr-H), 7.34-7.81(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable), 8.15(d, 1H, *J* = 7.5Hz, Fr-H). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 160.9, 158.9, 154.0, 144.9, 142.9, 137.2, 132.6, 129.2, 127.3, 126.6, 112.0, 107.1 ppm. IR (KBr, cm^{-1}): ν_{max} 3140(N-H), 1690(C=O),

1620(C=C), 1525(C=N). λ_{max} in nm (log ε_{max}): 220(4.02), 260(3.91), 300(3.46).

1-(5-Nitrofuran-2-yl)-[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one (5b). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 7.32-7.81(m, 6H, Ar-H & Fr-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 160.9, 158.9, 157.9, 150.8, 144.9, 137.2, 132.6, 129.2, 127.3, 126.6, 109.8, 109.5 ppm. IR (KBr, cm^{-1}): ν_{max} 3304(N-H), 1686(C=O), 1620(C=C). λ_{max} in nm (log ε_{max}): 210(4.01), 244(3.86), 273(4.11).

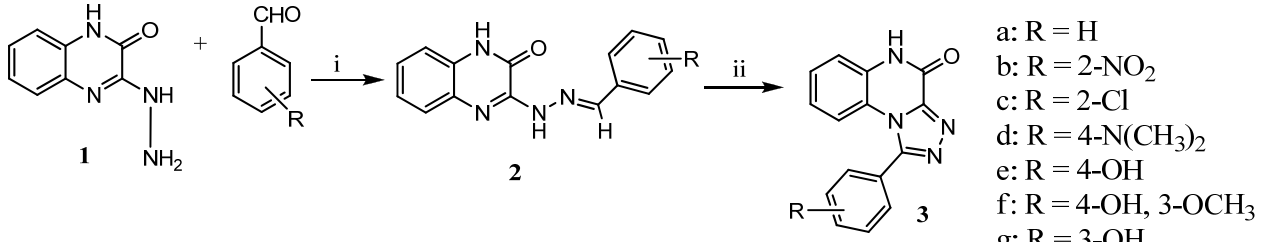
1-(5-Chlorofuran-2-yl)-[1,2,4]triazolo[4,3-a] quinoxalin-4(5*H*)-one (5c). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 6.54-7.07(dd, 2H, *J* = 3.4, 8.5Hz, Fr-H), 7.32-7.81(m, 4H, Ar-H), 8.00(s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 160.9, 158.9, 154.4, 144.9, 137.2, 135.7, 132.6, 129.2, 127.3, 126.6, 110.2, 102.1 ppm. IR (KBr, cm^{-1}): ν_{max} 3140(N-H), 1690 (C=O), 1620(C=C). λ_{max} in nm (log ε_{max}): 220(4.01), 275(3.88), 298(3.65).

1-(5-Methylfuran-2-yl)-[1,2,4]triazolo[4,3-a] quinoxalin-4(5*H*)-one (5d). ^{1}H-NMR (400 MHz, CH_3OH-d_4): δ 2.30(s, 3H, CH_3), 6.08-6.95 (dd, 2H, *J* = 3.5, 8.5Hz, Fr-H), 7.32-7.82 (m, 4H, Ar-H), 8.00 (s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (50 MHz, CH_3OH-d_4): δ 165.2(C=O), 160.9, 158.9, 152.2, 151.4, 144.9, 137.2, 132.6, 129.2, 127.3, 126.6, 107.8, 107.6, 13.7(CH_3) ppm. IR (KBr, cm^{-1}): ν_{max} 3140 (N-H), 1685 (C=O), 1612 (C=C). λ_{max} in nm (log ε_{max}): 220(3.97), 277(4.12), 315(4.00).

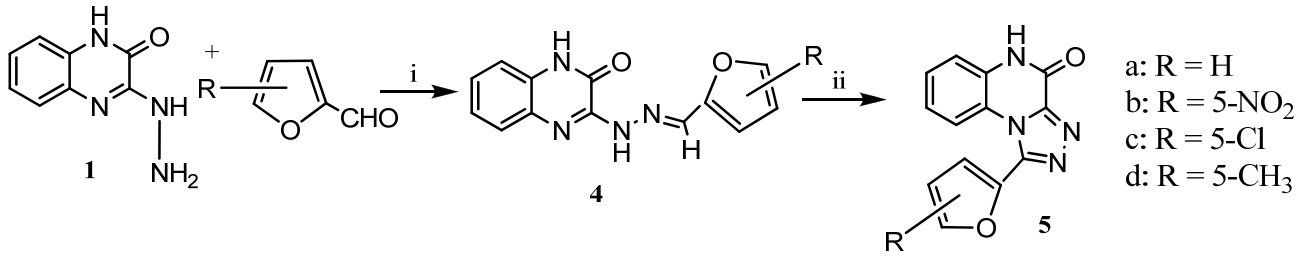
RESULTS AND DISCUSSION

3-Hydrazino-2-quinoxalinone **1** which was acting as the building block for the synthesis of all the hydrazones and triazoloquinoxalines, was itself prepared by hydrazinolysis of quinoxalin-2,3-dione using the method earlier described by Ajani *et al*. (2009). To a solution of quinoxalin-2,3-dione in hydrazine hydrate was added 50 ml of water and the resulting solution was reflux for 3 h. The mixture was allowed to cool and the formed precipitate was recrystallized from ethanol to afford 89% yield of **1**. The result of percentage yields and other physical parameters as well as elemental analysis is as shown in table 1. The condensation of **1** with benzaldehyde derivatives in the presence of ethanol gave the hydrazones **2a-h** which was subsequently thermally annelated at 200°C in the presence of ethylene glycol, a high boiling inert solvent, to afford crystalline products whose elemental analyses were consistent with the triazolo derivatives **3a-h** (Scheme 1). Part of the motivation for the conversion of hydrazones to triazolo products herein was based on the earlier findings by Rashed *et al*. (1990). In a like manner, exchanging of the aromatic aldehyde starting material with furfural led to the formation of hydrazones **4a-d** as the candidates for cyclization in order to obtain **5a-d** as the triazoloquinoxalinone, in good to excellent yields. The result of the reaction may be explained according to the mechanism illustrated in Schemes 1 and 2.

Compound **2e**, which was considered to be the typical representative of the hydrazones **2**, showed an infrared



Scheme 1: i = ethanol, 95°C, 3h reflux; ii = ethylene glycol, 200°C, 5h reflux



Scheme 2: i = ethanol, 95°C, 4h reflux; ii = ethylene glycol, 200°C, 5-7h reflux

Table 1. The Result of Physical Data and Elemental Analysis of the Synthesized Compounds 1-5d.

No	M.P. (°C)	Yield	R_f[a] Value	Mol. Formula (Mol. Weight)	Elem. Analy.% Calcd. (% Found) C	H	N
1	>360	89	0.63	$C_8H_8N_4O$ (176)	54.55(54.52)	4.55(4.57)	31.82(31.83)
2a	245-247	97	0.67	$C_{15}H_{12}N_4O$ (264)	68.18(68.25)	4.55(4.83)	21.21(21.09)
2b	260-261	91	0.64	$C_{15}H_{11}N_5O_3$ (309)	58.25(58.15)	3.56(3.61)	22.65(22.60)
2c	317-321	96	0.64	$C_{15}H_{11}N_4OCl$(298.5)	60.30(60.38)	3.69(3.62)	18.76(18.69)
2d	279-280	95	0.78	$C_{17}H_{17}N_5O$(307)	66.45(66.49)	5.54(5.48)	22.80(22.77)
2e	285(dec)	96	0.79	$C_{15}H_{12}N_4O_2$(280)	64.29(64.21)	4.29(4.38)	20.00(20.11)
2f	320(dec)	98	0.75	$C_{16}H_{14}N_4O_3$(310)	61.94(61.90)	4.52(4.59)	18.06(18.12)
2g	280-281	92	0.74	$C_{15}H_{12}N_4O_2$(280)	64.29(64.33)	4.29(4.17)	20.00(19.98)
2h	275-279	94	0.78	$C_{15}H_{12}N_4O_2$(280)	64.29(64.23)	4.29(4.34)	20.00(20.09)
3a	322-324	87	0.58	$C_{15}H_{10}N_4O$ (262)	68.70(68.85)	3.82(3.80)	21.37(21.44)
3b	329-330	87	0.77	$C_{15}H_9N_5O_3$ (307)	58.63(58.54)	2.93(2.69)	22.80(22.71)
3c	>360	81	0.81	$C_{15}H_9N_4OCl$(296.5)	60.71(60.54)	3.04(3.11)	18.89(18.68)
3d	347-349	79	0.66	$C_{17}H_{15}N_5O$(305)	66.89(66.97)	4.92(4.88)	22.95(22.90)
3e	355-357	80	0.59	$C_{15}H_{10}N_4O_2$(278)	64.75(64.67)	3.60(3.69)	20.14(20.29)
3f	>360	86	0.71	$C_{16}H_{12}N_4O_3$(308)	62.34(62.27)	3.90(3.14)	18.18(18.22)
3g	>360	81	0.64	$C_{15}H_{10}N_4O_2$(278)	64.75(64.79)	3.60(3.67)	20.14(20.11)
3h	315-317	74	0.59	$C_{15}H_{10}N_4O_2$(278)	64.75(64.70)	3.60(3.56)	20.14(20.09)
4a	216-219	77	0.61	$C_{13}H_{10}N_4O_2$(254)	61.42(61.38)	3.94(3.90)	22.05(21.99)
4b	282-284	95	0.50	$C_{13}H_9N_5O_4$(299)	52.17(52.22)	3.01(3.08)	23.41(23.39)
4c	301-303	90	0.66	$C_{13}H_9N_4O_2Cl$(288.5)	54.07(53.96)	3.12(3.01)	19.41(19.20)
4d	315-318	89	0.51	$C_{14}H_{11}N_4O_2$(267)	62.92(63.00)	4.12(4.19)	20.97(21.00)
5a	>360	88	0.54	$C_{13}H_8N_4O_2$(252)	61.90(61.98)	3.17(3.13)	22.22(22.16)
5b	>360	94	0.70	$C_{13}H_7N_5O_4$(297)	52.53(52.49)	2.36(2.41)	23.57(23.49)
5c	>360	97	0.63	$C_{13}H_7N_4O_2Cl$(286.5)	54.45(54.56)	2.44(2.35)	19.55(19.51)
5d	>360	72	0.44	$C_{14}H_9N_4O_2$(265)	63.40(63.44)	3.40(3.42)	21.13(21.18)

[a] Solvent System. $CHCl_3$:CH_3OH (9:1, v/v)

absorption band at ν 1685 cm^{-1} as a result of the presence of C=O of amide while the one observed at ν 1612 cm^{-1} and 1563 cm^{-1}depicted the presence of C=C of aromatic and C=N of hydrazone respectively. The highest frequency band noticed at ν 3241 cm^{-1} confirmed the presence of N-H of amide. The uv-visible absorption spectrum of **2e**, showed peaks at λ_{max} 212, 276, 352 and 376 nm and two noticeable shoulders at λ_{max} 308 and 394 nm respectively. The peak at 212nm is as a result of π→π* transition of C=C aromatic. ^{1}H-NMR spectrum of **2e** showed one –OH singlet at δ 5.35 ppm which disappeared upon D_2O shaking. The four aromatic protons of phenyl side chain gave rise to a multiplet at δ 6.85-7.78 ppm while four aromatic protons of benzofused quinoxaline was observed as a multiplet at 7.09-8.27. Also, the exchangeable protons of NH of hydrazone and that of amide both appeared down field of TMS scale at exactly δ 7.0 and 8.0 ppm respectively. Azomethine proton that confirmed the presence of hydrazone in **2e** was observed as a singlet at δ 8.54 ppm down field. Furthermore, ^{13}C-NMR spectrum of **2e** showed the presence of fifteen carbon atoms with carbon of hydrazone resonating at δ 146.8 ppm. All other signals were for the aromatic carbon atoms with sp^2 hybridization except δ 160.8 and 158.0 ppm which corresponded with carbonyl of amide and phenolic carbon atoms respectively.

Antimicrobial Screening

All the prepared compounds **1-5d** were screened for their antimicrobial activity against nine gram positive and five gram negative bacteria (Table 2) as well as one fungus *Candida albican* (Fig. 1). For comparison, the compounds were screened in vitro along side with streptomycin and fluconazole as the standard antibacterial and antifungal drugs respectively. The general sensitivity testing was carried out in DMSO at 1000µg/mL using agar well diffusion method while minimum inhibitory concentration (MIC) was determined using two-fold dilution method (Russell and Furr, 1977). From the result of the antibacterial screening (Table 2), it was observed that some of the compounds exhibited significant activity. For instance, **2e, 2f, 3f, 4b** were active on five gram positive and five gram negative bacteria; **1, 4b, 5c** were active on five gram positive and four gram negative bacteria. In a like fashion, **2g, 3b, 3e, 3g** inhibited the growth of five gram positive and three gram negative bacterial strains while **2c, 2d, 3d, 3h, 4d, 5b** inhibited growth of four gram positive and two gram negative bacteria. Although, **2h, 3a, 4c** had low activity on gram negative bacteria,

Table 2. Result of antibacterial Screening (Sensitivity testing) with zones of inhibition in (mm).

Bacteria → / Comp. No↓	*B.a*	*B.c*	*B.p*	*B.s*	*B.su*	*C.s*	*C.p*	*S.a*	*S.f*	*E.c*	*K.p*	*P.a*	*P.f*	*S.d*
1	10	10	10	11	15	R	R	R	R	14	12	10	9	R
2a	R	R	R	16	R	R	R	R	R	14	10	R	11	11
2b	R	15	R	18	20	R	R	R	R	25	8	10	R	12
2c	12	R	R	16	21	R	R	14	R	10	16	R	R	R
2d	15	25	R	31	30	R	R	R	R	18	R	11	R	R
2e	24	26	R	25	28	R	R	12	R	30	22	28	15	20
2f	22	12	R	18	R	7	9	R	R	12	15	R	R	R
2g	24	20	7	20	11	R	R	R	R	28	12	15	R	R
2h	18	18	14	15	11	5	R	R	R	16	14	R	R	R
3a	18	15	R	15	15	5	8	R	8	R	12	17	R	R
3b	13	20	R	13	16	R	R	8	R	9	16	14	R	R
3c	R	R	R	14	10	R	R	R	R	22	17	R	R	R
3d	11	8	R	10	11	R	R	R	R	19	19	R	R	R
3e	R	16	R	15	19	R	10	R	7	28	18	15	R	R
3f	13	13	R	12	18	R	R	R	7	17	23	15	13	11
3g	15	22	R	20	14	R	R	R	10	13	22	17	R	R
3h	18	20	15	21	R	R	R	R	R	14	12	R	R	R
4a	12	18	R	17	13	R	R	R	R	8	20	12	R	R
4b	18	R	R	12	15	4	8	R	R	21	13	13	R	19
4c	15	13	9	16	14	11	R	R	R	14	19	R	R	R
4d	17	23	8	28	R	R	R	R	R	13	R	11	R	R
5a	14	15	11	10	24	R	11	R	R	22	17	15	R	17
5b	21	18	R	12	19	R	R	R	R	19	15	R	R	R
5c	11	22	R	12	29	R	R	15	R	24	20	15	11	R
5d	13	20	R	17	20	R	R	R	R	20	11	14	R	R
str	24	20	18	15	19	21	13	27	30	R	R	13	14	13

B.a = Bacillus anthracis (LIO)$^{G+}$, *B.c = Bacillus cereus* (NCIB 6349)$^{G+}$, *B.p = Bacillus polymyxa* (LIO)$^{G+}$, *B.s = Bacillus stearothermophilus* (NCIB 8222)$^{G+}$, *B.su = Bacillus subtilis* (NCIB 3610)$^{G+}$, *C.s = Clostridium sporogenes* (LIO)$^{G+}$, *C.p = Corynebacterium pyogene* (LIO)$^{G+}$, *S.a = Staphylococcus aureus* (NCIB 8588)$^{G+}$, *S.f = Streptococcus faecalis* (NCIB775)$^{G+}$, *E.c = Escherichia coli* (NCIB 86)$^{G-}$, *K.p = Klebsiella pneumonia* (NCIB 418)$^{G-}$, *P.a = Pseudomonas aeruginosa* (NCIB 950)$^{G-}$, *P.f = Pseudomonas fluorescence* (NCIB 3756)$^{G-}$, *S.d = Shigella dysenteriae* (LIO)$^{G-}$; Str = Streptomycin, $^{G+}$ Gram positive, $^{G-}$ Gram negative, R = Bacteria are resistant to the compounds at 1000 µg/mL.

however, they inhibited the growth of six gram positive bacterial isolates. Streptomycin had broad activity spectrum on all gram positive and three gram negative organisms. Nevertheless, *E. coli* and *Klebsiella pneumonia* developed resistance against streptomycin while all the synthesized compounds were active on the two organisms. Due to variation in sensitivity testing result, minimum inhibitory concentration (MIC) test, which is defined as the lowest concentration of drug that completely inhibited the growth of the organism, was selectively carried out on four gram positive and two gram negative bacteria (Table 3). The MICs value for all the compounds varied between 7.8µg/mL and 125µg/mL while that of streptomycin standard was between 7.8 µg/mL and 15.6µg/mL. Compounds **3e, 3f, 3h**, had the same MIC range with streptomycin while **2e** was observed to be the only compound that had MIC value of 7.8µg/mL throughout. The results indicated that **2e** has a higher activity than streptomycin against most of the tested bacterial isolates.

The result of the antifungal activity was as shown in figure 1. It was noticed that **5c** competed favourable with fluconazole at 32 mm while all other compounds were not as active as fluconazole standard because their zones of inhibition varied between 19mm and 28mm.

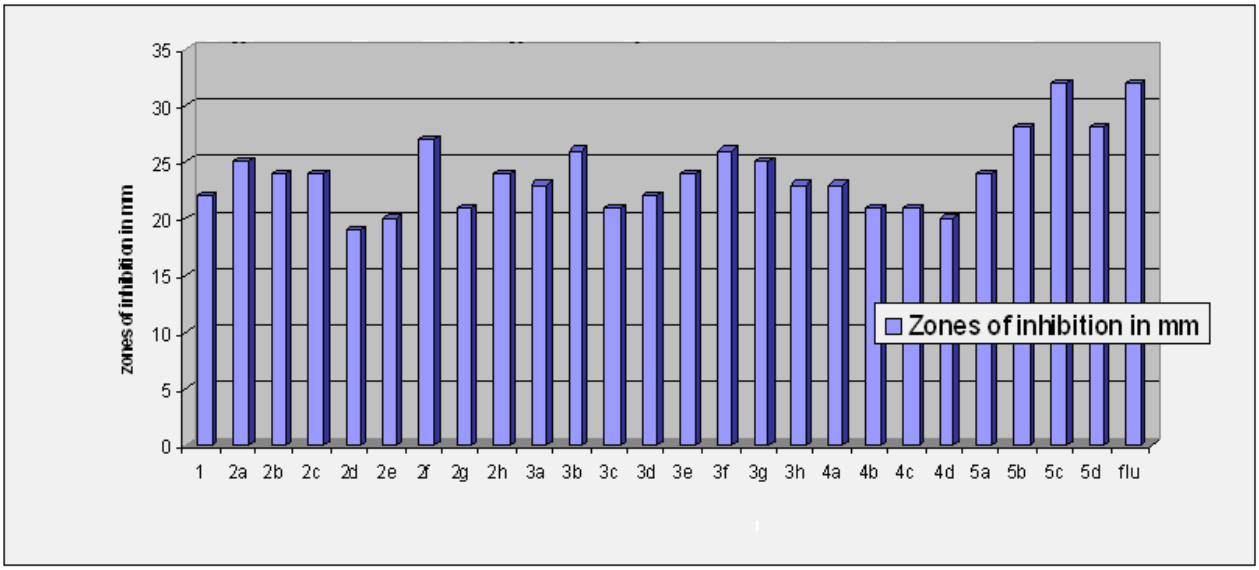
CONCLUSION

As envisaged from literature review, the thermal annelation of various hydrazones **2a-h** and **4a-4d** to give the corresponding [1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one **3a-3h** and **5a-d** respectively, was successful. Compounds **2e** and **5c** emerged as the most active antibacterial and antifungal agents respectively.

Table 3. Result of Minimum Inhibitory Concentration (MIC) test on some selected bacteria in µg/mL.

Bacteria → Comp. No↓	*Bacillus anthracis*	*Bacillus cereus*	*Bacillus Stearotherm.*	*Bacillus subtilis*	*Escherichia coli*	*Klebsiella pneumonia*
1	62.5	31.3	62.5	62.5	15.6	15.6
2a	R	R	15.6	R	7.8	31.3
2b	R	15.6	15.6	7.8	7.8	125.0
2c	31.3	R	31.3	15.6	31.3	31.3
2d	62.5	15.6	7.8	7.8	15.6	R
2e	7.8	7.8	7.8	7.8	7.8	7.8
2f	15.6	31.3	15.6	R	31.3	31.3
2g	7.8	15.6	15.6	62.5	7.8	31.3
2h	15.6	15.6	15.6	31.3	15.6	31.3
3a	7.8	15.6	15.6	15.6	R	31.3
3b	31.3	7.8	31.3	15.6	31.3	15.6
3c	R	R	15.6	31.3	7.8	7.8
3d	31.3	31.3	15.6	15.6	7.8	7.8
3e	R	7.8	15.6	15.6	7.8	15.6
3f	15.6	15.6	15.6	7.8	7.8	7.8
3g	31.3	7.8	31.3	7.8	31.3	7.8
3h	15.6	7.8	7.8	R	15.6	15.6
4a	31.3	15.6	15.6	31.3	62.5	7.8
4b	7.8	R	31.3	15.6	7.8	15.6
4c	15.6	31.3	7.8	15.6	15.6	7.8
4d	15.6	7.8	7.8	R	31.3	R
5a	15.6	15.6	31.3	7.8	7.8	7.8
5b	7.8	7.8	31.3	15.6	15.6	15.6
5c	31.3	15.6	15.6	7.8	7.8	7.8
5d	31.3	7.8	15.6	7.8	7.8	62.5
str	7.8	7.8	15.6	7.8	R	R

Str = Streptomycin, R = Bacteria are resistant to the compounds at 1000µg/mL.



Synthesized compounds (1-5d) and Fluconazole

Fig. 1. Result of antifungal activity with zones of inhibition in mm

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Received: May 4, 2009; Revised: June 30, 2009; Accepted: July 2, 2009