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Synthesis and Study of Antibacterial Activity of 1,4-Benzodioxinylisoxazole and 1,4-Benzodioxinylpyrazole Derivatives

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ABSTRACT

Since the presence of the 1,4-benzodioxane, isoxazole and pyrazole moiety seems to be responsible for the antibacterial property, the series of 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives have been synthesized, characterized and tested their antibacterial activity. The synthesis of new 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives was carried out by chalcone route. This route attracts attention because of its simple operating conditions and easy availability of the chemicals. The title compounds were screened for antibacterial activity. Among the synthesized compounds (4a-j) and (5a-j), some of title compounds exhibited significant activity and few compounds showed moderate and less activity against screened bacterial strains compared to standard. The structures of the title compounds were confirmed by Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (NMR) and mass spectroscopy methods. The synthesized compounds were tested for antibacterial activity. The synthesized compounds were screened for antibacterial activity.

Keywords: Chalcone, Antibacterial activity, 1,4-Benzodioxinylisoxazole, 1,4-Benzodioxinylpyrazole

INTRODUCTION

In the course of searching for new drugs against diseases, the discovery, development and synthesis of new efficiency, active and less toxic molecules have been the object of many research works [1-5]. In this context, many structures of aromatic heterocyclic compounds have been investigated such as isoxazole [6], pyrazole [7], triazole [8] and tetrazole [9] due to their biological importance [10-12]. Isoxazole derivatives attracted attention due to their diverse pharmaceutical properties. Isoxazole and its derivatives are important five membered promising nitrogen oxygen containing heterocyclic compounds [13] and they showed good biological activities such as antidiabetic, analgesic, antiarrhythmic, anti-inflammatory, antifungal and antiviral activity [14-17]. They exhibited potent and selective antagonism of the N-methyl-D-aspartate (NMDA) receptor [18] and anti-HIV activity [19].

In particular, heterocyclic compounds containing pyrazole moieties occupy a prominent place due to their different and important biological activity [20]. Pyrazole derivatives are the subject of many research studies on their widespread potential biological activities such as anticancer [21], antimicrobial [22,23], enzyme inhibitors [24], antiviral [25], antidepressant [26], insecticides and fungicides [27] and other activities. In view of this, the research effort has been initiated towards synthesis and study of antibacterial activity of 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives.

MATERIALS AND METHODS

All the reagents and chemicals were purchased from Merck Chemicals used without further purification. Melting points were taken in open capillary tubes and are uncorrected. TLC is performed with E. Merck precoated silica gel plates (60F-254) with iodine as a developing agent. Acme, India silica gel, 60-120 mesh for column chromatography is used. IR spectra in KBr were recorded on Perkin-Elmer model 1310 spectrometers. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra using trimethylsilane as an internal reference were recorded on Bruker spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Water- Q-Tof Ultima Mass Spectrometer. Micro analytical data were obtained by elemental-Vario EL-III.

General procedure for the synthesis of chalcone

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)ethanone (1.78 g, 10 mmol) (1) and substituted aldehydes (2a-j) (10 mmol) were stirred in 30% methanolic NaOH and water mixture at 15-30°C for 4-6 h. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from ethanol.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-phenylprop-2-en-1-one (3a)

Color: Yellow solid; Yield: 81.20%; m.p.: 65-67°C; IR(KBr)$_{vmax}$: 3140-2952 (Ar-CH), 1667 (C=O), 1583 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.96 (d, 1H, *β*-CH), 7.78 (d, 2H, Ar-H), 7.51 (d, 2H, Ar-H), 7.46 (dd, 1H, Ar-H), 7.38 (d, 1H, *α*-CH), 7.10 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.21 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.96 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.12 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 145.1, 135.2, 128.6, 128.5, 127.9, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2; MS, *m*/*z*: 266.01 (*M*+). *Anal*. *Calcd*. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.65; H, 5.32%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(p-tolyl)prop-2-en-1-one (3b)

Color: Yellow solid; Yield: 87.30%; m.p.: 71-73°C; IR (KBr)$_{vmax}$: 3141-2942 (Ar-CH), 1661 (C=O), 1589 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.91 (d, 1H, *β*-CH), 7.71 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H), 7.35 (d, 1H, *α*-CH), 7.28 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.90 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.16 (m, 4H, 1,4-dioxane –CH_2-), 2.40 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 145.1, 137.6, 132.2, 128.9, 128.5, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2, 21.3; MS, *m*/*z*: 280.06 (*M*+). *Anal*. *Calcd*. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.15; H, 5.73%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (3c)

Color: Yellow solid; Yield: 94.10%; m.p.: 84-86°C; IR (KBr)$_{vmax}$: 3154-2938 (Ar-CH), 1667 (C=O), 1586 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.01 (d, 1H, *β*-CH), 7.85 (d, 2H, Ar-H), 7.69 (d, 2H, Ar-H), 7.23 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.22 (d, 1H, *α*-CH), 7.19 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.86 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.15 (m, 4H, 1,4-dioxane –CH_2-), 3.71 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 159.8, 156.5, 149.8, 145.1, 130.2, 127.5, 121.4, 121.3, 122.1, 114.2, 112.0, 106.8, 64.2, 55.8; MS, *m*/*z*: 296.14 (*M*+). *Anal*. *Calcd*. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.92; H, 5.45%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3d)

Color: Yellow solid; Yield: 65.00%; m.p.: 90-92°C; IR (KBr)$_{vmax}$: 3151-2937 (Ar-CH), 1658 (C=O), 1579 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.79 (d, 1H, *β*-CH), 7.67 (s, 2H, Ar-H), 7.26 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.21 (d, 1H, *α*-CH), 7.11 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.89 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.10 (m, 4H, 1,4-dioxane –CH_2-), 3.87 (s, 9H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 153.0, 149.8, 145.1, 138.4, 126.4, 121.4, 121.3, 122.1, 112.0, 106.8, 103.8, 64.2, 60.8, 56.1; MS, *m*/*z*: 296.14 (*M*+). *Anal*. *Calcd*. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.45; H, 5.64%.

3-(4-chlorophenyl)-1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)prop-2-en-1-one (3e)

Color: Gray solid; Yield: 86.57%; m.p.: 71-73°C; IR (KBr)$_{vmax}$: 3156-2934 (Ar-CH), 1655 (C=O), 1575 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.71 (d, 1H, *β*-CH), 7.92 (d, 2H, Ar-H), 7.62 (d, 2H, Ar-H), 7.23 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.21 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.01 (d, 1H, *α*-CH), 6.93 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.14 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 145.1, 133.5, 133.3, 129.0, 128.7, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2; MS, *m*/*z*: 300.11 (*M*+). *Anal*. *Calcd*. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 67.85; H, 4.31%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(4-fluorophenyl)prop-2-en-1-one (3f)

Color: Light yellow solid; Yield: 80.09%; m.p.: 78-80°C; IR (KBr)$_{vmax}$: 3168-2944 (Ar-CH), 1666 (C=O), 1588 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.84 (d, 1H, *β*-CH), 7.82 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.26 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, *α*-CH), 7.09 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.93 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.22 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 162.1, 156.5, 149.8, 145.1, 130.8, 130.4, 122.1, 121.4, 121.3, 115.4, 112.0, 106.8, 64.2; MS, *m*/*z*: 284.00 (*M*+). *Anal*. *Calcd*. for $C_{17}H_{13}FO_3$: C, 71.82; H, 4.61. Found: C, 71.78; H, 4.63%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(4-nitrophenyl)prop-2-en-1-one (3g)

Color: Light yellow solid; Yield: 79.20%; m.p.: 87-89°C; IR (KBr)$_{vmax}$: 3161-2940 (Ar-CH), 1657 (C=O), 1578 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.81 (d, 2H, Ar-H), 7.80 (d, 1H, *β*-CH), 7.56 (d, 2H, Ar-H), 7.31 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.19 (d, 1H, *α*-CH), 7.18 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.79 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.13 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 147.1, 145.1, 141.3, 129.0, 123.8, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2; MS, *m*/*z*: 311.04 (*M*+). *Anal*. *Calcd*. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.56; H, 4.25; N, 4.54%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(3-nitrophenyl)prop-2-en-1-one (3h)

Color: Brown solid; Yield: 64.15%; m.p.: 86-88°C; IR (KBr)$_{vmax}$: 3168-2945 (Ar-CH), 1665 (C=O), 1586 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.84 (d, 1H, Ar-H), 7.72 (d, 1H, *β*-CH), 7.46 (d, 1H, Ar-H), 7.24 (d, 1H, Ar-H), 7.16 (d, 1H, Ar-H), 7.15 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.10 (d, 1H, *α*-CH), 7.12 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.83 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.02 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 147.8, 141.5, 137.7, 134.6, 129.5, 123.1, 122.7, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2; MS, *m*/*z*: 311.02 (*M*+). *Anal*. *Calcd*. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.54; H, 4.22; N, 4.51%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (3i)

Color: Yellow solid; Yield: 80.14%. m.p.: 96-98°C; IR (KBr)$_{vmax}$: 3165-2941 (Ar-CH), 1662 (C=O), 1584 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.34-7.60 (m, 7H, Naphthalene-H), 7.69 (d, 1H, *β*-CH), 7.34 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.25 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, *α*-CH), 6.80 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.12 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=196.1, 156.5, 149.8, 135.8, 133.6, 133.5, 132.0, 128.8, 128.3, 126.9, 126.3, 126.0, 124.0, 122.9, 122.1, 121.4, 121.3, 112.0, 106.8, 64.2; MS, *m*/*z*: 316.05 (*M*+). *Anal*. *Calcd*. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.70; H, 5.14%.

1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-(thiophen-2-yl)prop-2-en-1-one (3j)

Color: Brick red solid; Yield: 84.00%; m.p.: 62-64°C; IR (KBr)$_{vmax}$: 3163-2947 (Ar-CH), 1659 (C=O), 1563 (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.72 (d, 1H, *β*-CH), 7.59-7.30 (m, 3H, Thiophene-H), 7.21 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.15 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.10 (d, 1H, *α*-CH), 6.97 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 4.21 (m, 4H, 1,4-dioxane –CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=189.7, 156.5, 149.8, 140.3, 134.1, 130.5, 129.1, 128.3, 127.3, 122.1, 121.4, 112.0, 106.8, 64.2; MS, *m*/*z*: 316.05

(*M+*). *Anal*. *Calcd*. for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 66.12; H, 4.40%.

General procedure for synthesis of 3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)isoxazole derivatives

Substituted 1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-prop-2-en-1-one (5 mmol), hydroxylamine hydrochloride 2 (0.36 g, 5.2 nmol) and ethanol (10 ml) were added to a 50 mL round-bottom flask. The mixture was then stirred at 60°C for 2 h. After completion of the reaction, the mixture was then cooled to room temperature. The precipitated products were filtered and recrystallized from ethanol.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenylisoxazole (4a)

Color: Light yellow solid; m.p. 92-94°C; IR $(KBr)_{vmax}$: 3054 (C-H in Ar-H), 2916 (C-H), 1638 (C=N-O), 1602 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.17 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.43 (dd, 1H, Ar-H), 7.28 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.15 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.96 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.72 (s, 1H, =CH-), 4.22 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.1, 162.4, 147.4, 150.3, 129.5, 128.5, 126.1, 125.7, 119.1, 110.3, 108.5, 64.4; MS, m/z: 279.02 (M+). *Anal*. *Calcd*. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.14; H, 4.65; N, 5.00%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(p-tolyl)isoxazole (4b)

Color: Light yellow solid; m.p.: 115-117°C; IR $(KBr)_{vmax}$: 3059 (C-H in Ar-H), 2912 (C-H), 1633 (C=N-O), 1605 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.12 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.24 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.13 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.91 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.75 (s, 1H, =CH-), 4.14 (m, 4H, 1,4-dioxane –CH2-), 2.43 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 150.7, 147.2, 131.7, 129.5, 125.2, 124.9, 123.6, 119.7, 110.7, 108.1, 98.3, 64.2, 21.3; MS, m/z: 293.03 (M+). *Anal*. *Calcd*. for $C_{15}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.71; H, 5.15; N, 4.78 %.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-methoxyphenyl)isoxazole (4c)

Color: Light brown solid; m.p. 102-104°C; IR $(KBr)_{vmax}$: 3065 (C-H in Ar-H), 2914 (C-H), 1635 (C=N-O), 1614 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.07 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.21 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.18 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.88 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.67 (s, 1H, =CH-), 4.11 (m, 4H, 1,4-dioxane –CH2-), 3.79 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 160.6, 150.7, 147.2, 127.3, 125.2, 119.7, 118.9, 114.8, 110.7, 108.1, 98.3, 64.2, 55.8; MS, m/z: 309.03 (M+). *Anal*. *Calcd*. for $C_{15}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.83; H, 4.82; N, 4.56%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxyphenyl)isoxazole (4d)

Color: Wood colour solid; m.p. 110-112°C; IR $(KBr)_{vmax}$: 3065 (C-H in Ar-H), 2914 (C-H), 1635 (C=N-O), 1614 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.23 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.99 (d, 2H, Ar-H), 6.92 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.61 (s, 1H, =CH-), 4.21 (m, 4H, 1,4-dioxane –CH2-), 3.75 (s, 9H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 153.1, 150.7, 147.2, 139.2, 125.2, 124.6, 119.7, 110.7, 108.1, 101.2, 98.3, 64.2, 60.8, 56.1; MS, m/z: 369.15 (M+). *Anal*. *Calcd*. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.07; H, 5.19; N, 3.74%.

5-(4-chlorophenyl)-3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)isoxazole (4e)

Color: Brown solid; m.p. 99-101°C; IR $(KBr)_{vmax}$: 3057 (C-H in Ar-H), 2922 (C-H), 1642 (C=N-O), 1625 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.01 (d, 2H, Ar-H), 7.41 (d, 2H, Ar-H), 7.26 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.15 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.82 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.63 (s, 1H, =CH-), 4.19 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 150.7, 147.2, 134.3, 129.3, 125.2, 124.9, 124.7, 119.7, 110.7, 108.1, 98.3, 64.2; MS, m/z: 313.01 (M+). *Anal*. *Calcd*. for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: C, 65.02; H, 3.82; N, 4.47%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-fluorophenyl)isoxazole (4f)

Color: Brown solid; m.p.: 118-120°C; IR $(KBr)_{vmax}$: 3051 (C-H in Ar-H), 2925 (C-H), 1645 (C=N-O), 1626 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.79 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.29 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.12 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.85 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.69 (s, 1H, =CH-), 4.26 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.9, 162.0, 150.7, 147.2, 127.7, 125.2, 122.2, 119.7, 116.0, 110.7, 108.1, 98.3, 64.2; MS, m/z: 297.03 (M+). *Anal*. *Calcd*. for $C_{17}H_{12}FNO_3$: C, 68.68; H, 4.07; N, 4.71. Found: C, 68.65; H, 4.02; N, 4.76%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-nitrophenyl)isoxazole (4g)

Color: Brown solid; m.p.: 126-128°C; IR $(KBr)_{vmax}$: 3064 (C-H in Ar-H), 2932 (C-H), 1654 (C=N-O), 1630 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.24 (d, 2H, Ar-H), 7.32 (d, 2H, Ar-H), 7.16 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.04 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.94 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.45 (s, 1H, =CH-), 4.14 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 150.7, 147.9, 147.2, 132.7, 125.2, 124.5, 124.4, 119.7, 110.7, 108.1, 98.3, 64.2; MS, m/z: 324.04 (M+). *Anal*. *Calcd*. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 62.92; H, 3.70; N, 8.66%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(3-nitrophenyl)isoxazole (4h)

Color: Gray solid; m.p.: 120-122°C; IR $(KBr)_{vmax}$: 3067 (C-H in Ar-H), 2939 (C-H), 1650 (C=N-O), 1635 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.34 (d, 1H, Ar-H), 8.26 (d, 1H, Ar-H), 8.14 (d, 1H, Ar-H), 7.86 (d, 1H, Ar-H), 7.35 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.26 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.90 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.40 (s, 1H, =CH-), 4.21 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 150.7, 148.4, 147.2, 131.3, 131.2, 130.1, 125.2, 123.9, 122.8, 119.7, 110.7, 108.1, 98.3, 64.2; MS, m/z: 324.00 (M+). *Anal*. *Calcd*. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 62.91; H, 3.71; N, 8.62%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(naphthalen-1-yl)isoxazole (4i)

Color: Brown Gummy; m.p.: 143-145°C; IR $(KBr)_{vmax}$: 3057 (C-H in Ar-H), 2931 (C-H), 1655 (C=N-O), 1640 (C-C in Ar); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.30-7.46 (m, 7H, Naphthalene-H), 7.31 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.20 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.84 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.54 (s, 1H, =CH-), 4.18 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=169.3, 162.0, 150.7, 147.2, 136.0, 134.2, 132.7, 128.3, 126.3, 125.4, 125.2, 119.7, 118.1, 110.7, 108.1, 98.3, 64.2; MS, m/z: 329.04 (M+). *Anal*. *Calcd*. for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.53; H, 4.62; N, 4.22%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(thiophen-2-yl)isoxazole (4j)

Color: Light Brown Solid; m.p.: 109-111°C; IR $(KBr)_{vmax}$: 3065 (C-H in Ar-H), 2938 (C-H), 1650 (C=N-O), 1646 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.52-7.34 (m, 3H, Thiophene-H), 7.26 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.18 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.91 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.66 (s, 1H, =CH-), 4.22 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=162.0, 158.9, 150.7, 147.2, 133.7, 128.0, 125.2, 124.0, 122.5, 119.7, 110.7, 108.1, 98.3, 64.2; MS, m/z: 285.00 (M+). *Anal*. *Calcd*. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 63.11; H, 3.86; N, 4.95%.

General procedure for synthesis of 3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-1H-pyrazole derivatives

A mixture of Substituted 1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-3-prop-2-en-1-one (2a-j) (5 mmol) and hydrazine hydrate (0.26 g, 5.2 mmol) in absolute ethanol was refluxed for 4-6 hrs. The reaction mixture was cooled to °C with ice cold water. The precipitate thus obtained was filtered, washed with water and purified by recrystallization from ethanol.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenyl-1H-pyrazole (5a)

Color: Yellow solid; m.p.: 104-106°C; IR $(KBr)_{vmax}$: 3335 (NH), 3060 (C-H in Ar-H), 2919 (C-H), 1610 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.11 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.48 (dd, 1H, Ar-H), 7.42 (s, 1H, NH), 7.22 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.19 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.88 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.76 (s, 1H, =CH-), 4.26 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 147.7, 147.2, 133.0, 129.2, 128.7, 127.5, 127.2, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 278.17 (M+). *Anal*. *Calcd*. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.35; H, 5.04; N, 10.09%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(p-tolyl)-1H-pyrazole (5b)

Color: Light yellow solid; m.p.: 118-120°C; IR $(KBr)_{vmax}$: 3331 (NH), 3062 (C-H in Ar-H), 2913 (C-H), 1614 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.18 (d, 2H, Ar-H), 7.62 (d, 2H, Ar-H), 7.48 (s, 1H, NH), 7.25 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.80 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.72 (s, 1H, =CH-), 4.23 (m, 4H, 1,4-dioxane –CH2-), 2.24 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 147.7, 147.2, 131.7, 130.0, 129.5, 127.2, 125.7, 119.7, 110.7, 108.1, 99.7, 64.2, 21.3; MS, m/z: 292.10 (M+). *Anal*. *Calcd*. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.94; H, 5.56; N, 9.55%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-methoxyphenyl)-1H-pyrazole (5c)

Color: Congo Red solid; m.p.: 125-127°C; IR $(KBr)_{vmax}$: 3325 (NH), 3057 (C-H in Ar-H), 2917 (C-H), 1615 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.08 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 7.41 (s, 1H, NH), 7.20 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.15 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.87 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.76 (s, 1H, =CH-), 4.23 (m, 4H, 1,4-dioxane –CH2-), 3.78 (s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=160.6, 150.7, 147.7, 147.2, 128.5, 127.2, 128.5, 125.3, 119.7, 114.8, 108.1, 110.7, 99.7, 64.2, 55.8; MS, m/z: 308.07 (M+). *Anal*. *Calcd*. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.18; H, 5.24; N, 9.05%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (5d)

Color: Brick Red solid; m.p.: 135-137°C; IR $(KBr)_{vmax}$: 3328 (NH), 3055 (C-H in Ar-H), 2913 (C-H), 1619 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.64 (d, 2H, Ar-H), 7.44 (s, 1H, NH), 7.24 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.12 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.92 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.69 (s, 1H, =CH-), 4.10 (m, 4H, 1,4-dioxane –CH2-), 3.85 (s, 9H, OCH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=153.1, 150.7, 147.7, 147.2, 139.2, 127.3, 127.2, 119.7, 110.7, 108.1, 100.7, 99.7, 64.2, 60.8, 56.1; MS, m/z: 368.10 (M+). *Anal*. *Calcd*. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.25; H, 5.45; N, 7.64%.

5-(4-chlorophenyl)-3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-1H-pyrazole (5e)

Color: Brown solid; m.p.: 114-116°C; IR $(KBr)_{vmax}$: 3322 (NH), 3052 (C-H in Ar-H), 2919 (C-H), 1625 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.01 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 7.40 (s, 1H, NH), 7.22 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.14 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.95 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.64 (s, 1H, =CH-), 4.14 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 147.7, 147.2, 134.3, 131.1, 129.3, 128.9, 127.2, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 312.02 (M+). *Anal*. *Calcd*. for $C_{17}H_{13}ClN_2O_2$: C, 65.29; H, 4.19; N, 8.96. Found: C, 65.24; H, 4.13; N, 8.92%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-fluorophenyl)-1H-pyrazole (5f)

Color: Wood colour solid; m.p.: 140-142°C; IR $(KBr)_{vmax}$: 3333 (NH), 3060 (C-H in Ar-H), 2924 (C-H), 1620 (C-C in Ar); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.12 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H), 7.42 (s, 1H, NH), 7.25 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.19 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.92 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.60 (s, 1H, =CH-), 4.21 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=162.9, 150.7, 147.7, 147.2, 130.6, 128.6, 127.2, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 296.15 (M+). *Anal*. *Calcd*. for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; N, 9.45. Found: C, 68.94; H, 4.44; N, 9.42%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(4-nitrophenyl)-1H-pyrazole (5g)

Color: Light yellow solid; m.p.: 134-136°C; IR $(KBr)_{vmax}$: 3330 (NH), 3062 (C-H in Ar-H), 2922 (C-H), 1624 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.10 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.40 (s, 1H, NH), 7.22 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.12 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.88 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.63 (s, 1H, =CH-), 4.16 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 147.7, 147.2, 147.9, 139.1, 127.2, 126.2, 124.4, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 323.04 (M+). *Anal*. *Calcd*. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00. Found: C, 63.14; H, 4.07; N, 13.03%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(3-nitrophenyl)-1H-pyrazole (5h)

Color: Light yellow solid; m.p. 119-121°C; IR $(KBr)_{vmax}$: 3328 (NH), 3066 (C-H in Ar-H), 2928 (C-H), 1622 (C-C in Ar); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.30 (d, 1H, Ar-H), 8.22 (d, 1H, Ar-H), 8.17 (d, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 7.44 (s, 1H, NH), 7.30 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.21 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.93 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.44 (s, 1H, =CH-), 4.11 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 148.4, 147.7, 147.2, 133.9, 133.6, 130.6, 127.2, 123.9, 122.7, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 323.07 (M+). *Anal*. *Calcd*. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00. Found: C, 63.11; H, 4.09; N, 13.01%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(naphthalen-1-yl)-1H-pyrazole (5i)

Color: Yellow solid; m.p.: 133-135°C; IR (KBr)$_{vmax}$: 3336 (NH), 3069 (C-H in Ar-H), 2924 (C-H), 1625 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.34-7.42 (m, 7H, Naphthalene-H), 7.37 (s, 1H, NH), 7.33 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.22 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.80 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.52 (s, 1H, =CH-), 4.13 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 148.7, 147.7, 147.2, 140.6, 134.2, 132.7, 128.3, 127.2, 126.3, 125.4, 123.1, 119.7, 110.7, 108.1, 99.7, 64.2; MS, m/z: 328.10 (M+). *Anal*. *Calcd*. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.82; H, 4.94; N, 8.55%.

3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-(thiophen-2-yl)-1H-pyrazole (5j)

Color: Brick Red solid; m.p. 117-119°C; IR (KBr)$_{vmax}$: 3331 (NH), 3067 (C-H in Ar-H), 2921 (C-H), 1622 (C-C in Ar); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.50-7.33 (m, 3H, Thiophene-H), 7.31 (s, 1H, NH), 7.24 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 7.10 (d, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.78 (s, 1H, 2,3-dihydrobenzo[1,4]dioxine Ar-H), 6.62 (s, 1H, =CH-), 4.28 (m, 4H, 1,4-dioxane –CH2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.7, 147.2, 146.6, 139.9, 137.7, 131.9, 128.6, 128.0, 127.2, 119.7, 110.7, 108.1, 100.7, 64.2; MS, m/z: 284.03 (M+). *Anal*. *Calcd*. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.34; H, 4.20; N, 9.83%.

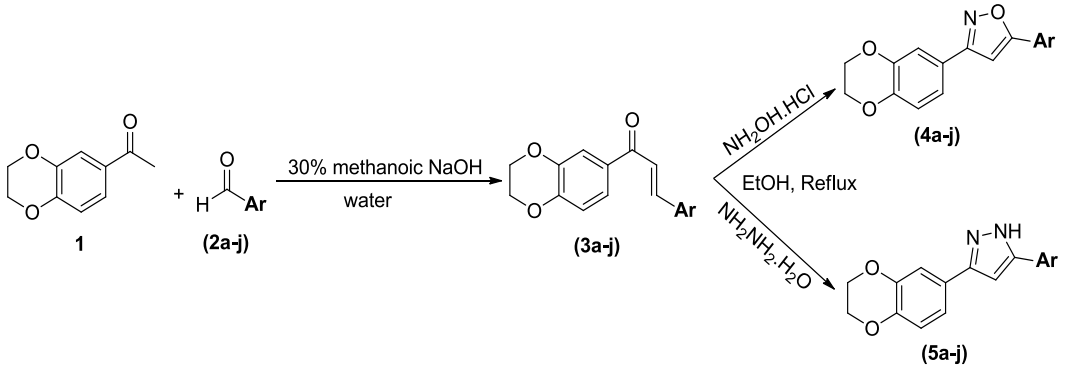
Antibacterial study

The antibacterial assay was performed by agar disk diffusion method [28,29]. For antibacterial activity, the molten Mueller–Hinton Agar (HiMedia) was inoculated with the 100 µl of the inoculum (1.5×10^8 Cfu/ml) and poured into the sterile petri plates (HiMedia). For agar disk diffusion method, the disk (0.7 cm) (Hi-Media) was saturated with 100 µl of 10.0 mg/ml of the test compound in the Dimethylformamide (DMF), allowed to dry and was introduced on the upper layer of the seeded agar plate. The plates containing test compounds were incubated overnight at 37°C for 24 h. Antibacterial activity of all the synthesized compounds was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi antibiotic zone scale). The medium with Dimethylformamide (DMF) as solvent was used as a negative control whereas media with Gentamicin (standard antibacterial drug) was used as positive control. The experiments were performed in triplicates.

RESULTS AND DISCUSSION

Chemistry

The synthesis of new 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives was carried out by chalcone route (Scheme 1). The benzylidene acetophenones (chalcones) (3a–j) were prepared in high yields by Claisen Schmidt reaction of 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone (1) with substituted benzaldehydes (2a-j) in the presence of 30% methanolic NaOH and water. The structures of the chalcones were confirmed by IR and NMR spectral studies. IR spectra of compounds (3a–j) showed the C=C stretching frequency in the range 1607-1575 cm^{-1} and ^{1}H-NMR showed the absence of aldehyde proton at 9.83 ppm. In the next step, the cyclization of compounds (3a–j) with hydroxylamine hydrochloride and phenyl hydrazine in absolute ethanol obtained the corresponding isoxazoles (4a–j) and pyrazole derivatives (5a–j) [30]. The structures of the compounds (4a–j) and (5a–j) were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analysis data. The synthesized compounds were screened for antibacterial activity. The results are summarized in the given Table 1.



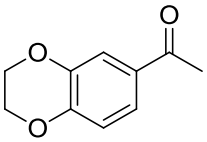
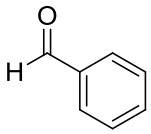
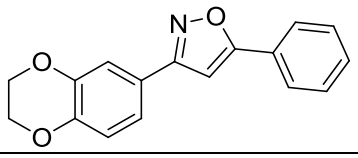
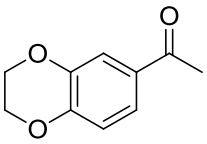
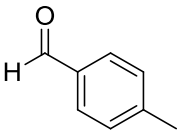
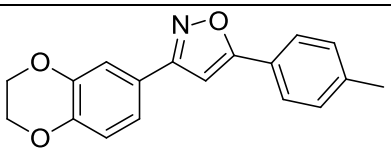
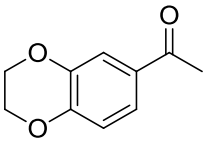
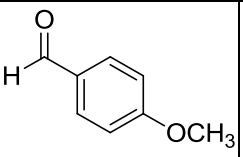
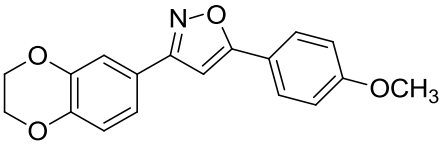
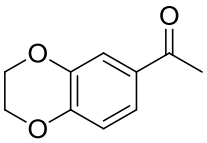
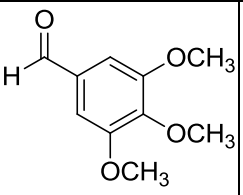
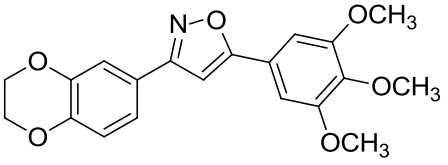
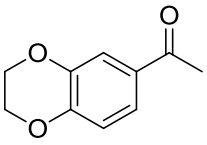
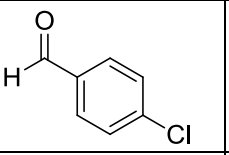
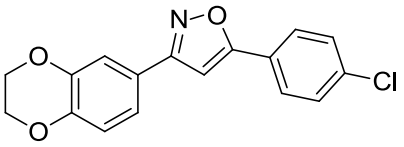
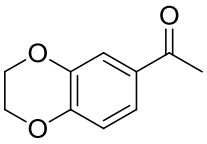
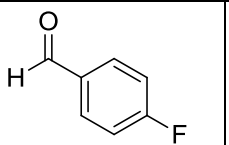
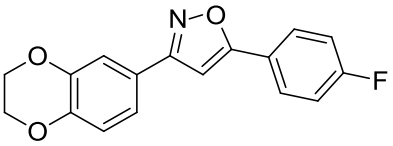
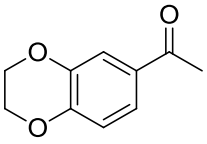
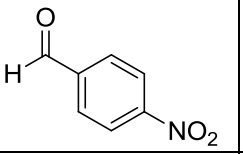
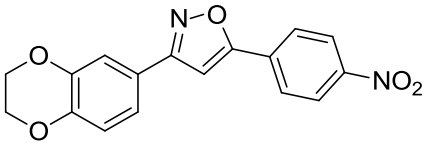
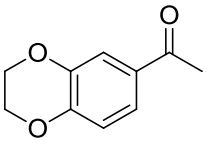
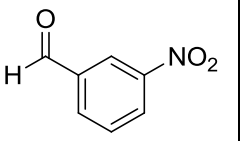
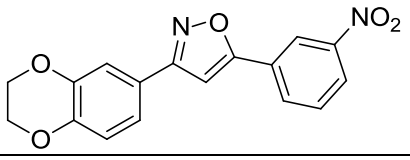
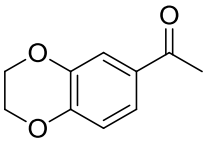
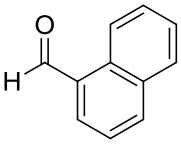
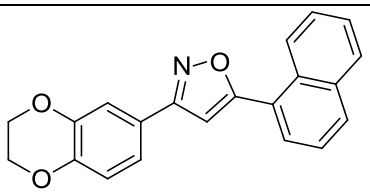
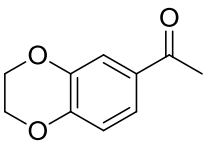
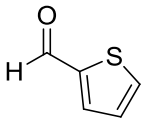
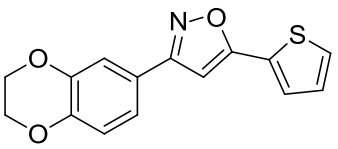
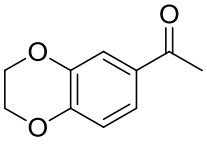
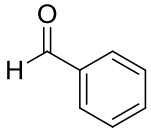
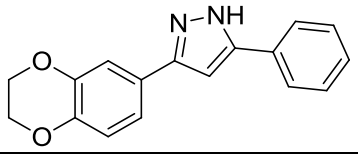
Scheme 1: Synthetic protocol for the synthesis of 1,4-benzodioxinylisoxazole (4a–j) and 1,4-benzodioxinylpyrazole derivatives (5a–j)

Antibacterial study

The newly synthesized compounds 4a–j and 5a–j were screened for antibacterial activity according to the above mentioned procedure. The four bacterial strains were treated with these compounds in Minimum Inhibitory Concentration (MIC) (mg/ml). Gentamicin was used as a standard. The four bacterial strain used in the present investigation were *Escherichia coli, Bacillus subtilis, Staphylococcus auerus and Salmonella typhi*. Most notably, 1,4-benzodioxinylisoxazole compounds 4g, 4h and 4i had comparable antibacterial effect on *E. coli*, 4a and 4e showed considerable activity on *B. subtilis* and 4f and 4h exhibited significant antibacterial efficacy on *S. typhi* bacterial strain.

Other compounds showed low activity. In 1,4-benzodioxinylpyrazole derivatives 5e, 5h on *E. coli*, 5a, 5g on *B. subtilis* and 5c, 5f, 5g on *S. typhi* bacterial strains respectively showed moderate antibacterial activity. Compounds 5d on *E. coli*, 5d, 5e, 5f on *B-subtilis* and 5i on *S. auerus* exhibited good antibacterial effect. The remaining compounds did not show any significant antibacterial activity (Table 2).

Table 1: Screened synthesized compounds for antibacterial activity

Entry	Acetophenone	Aldehyde	Compounds	Product	Yield (%)
1			**4a**		73.00
2			**4b**		71.00
3			**4c**		70.00
4			**4d**		73.00
5			**4e**		74.00
6			**4f**		69.00
7			**4g**		67.00
8			**4h**		64.00
9			**4i**		70.00
10			**4j**		65.00
11			**5a**		72.00

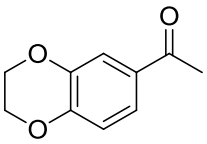
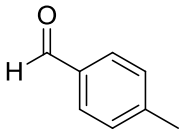
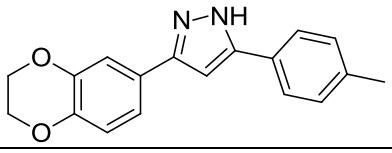
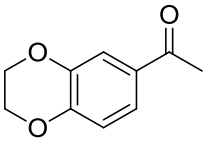
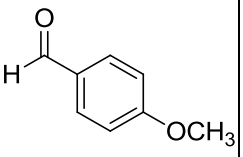
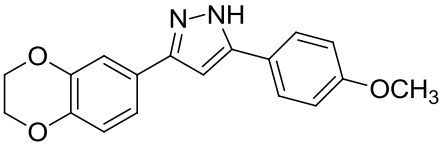
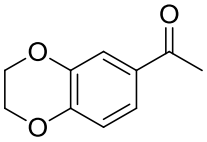
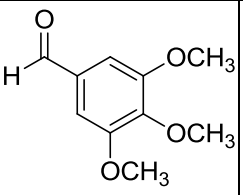
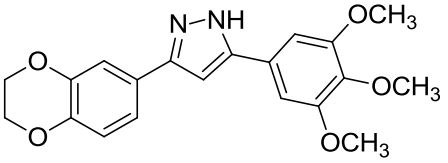
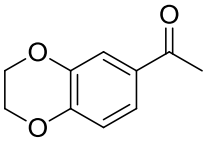
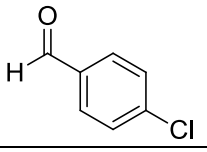
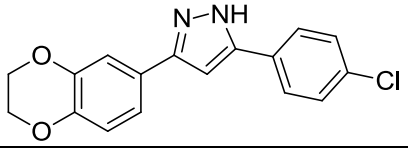
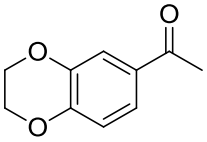
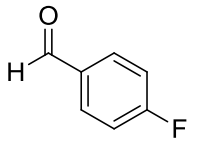
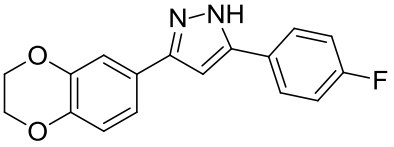
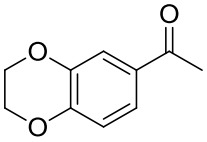
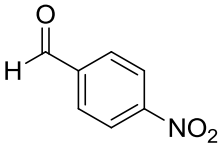
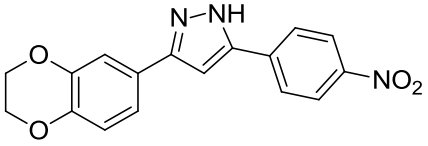
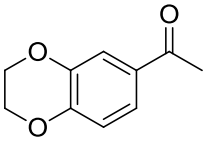
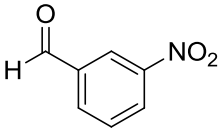
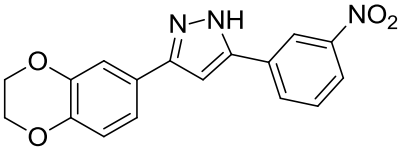
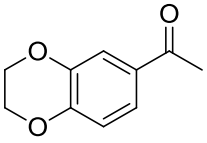
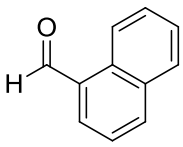
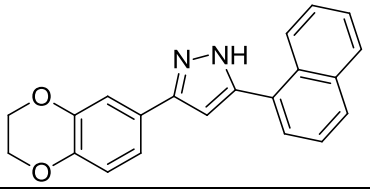
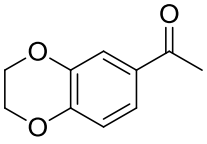
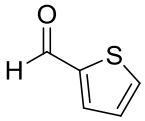
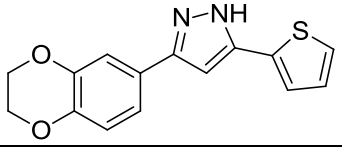
12			**5b**		76.00
13			**5c**		67.00
14			**5d**		73.00
15			**5e**		78.00
16			**5f**		71.00
17			**5g**		74.00
18			**5h**		63.00
19			**5i**		72.00
20			**5j**		69.00

Table 2: Antibacterial data of the compounds (4a–j) in MIC (mg/ml)

Comp. No./Bacterial strain	*Escherichia coli*	*Bacillus subtilis*	*Staphylococcus auerus*	*Salmonella typhi*
Gentamicin	25 ± 0.577	25 ± 0.76	19 ± 0.55	23.5 ± 0.40
4a	7 ± 0.88	19 ± 0.3	12 ± 0.41	5 ± 0.25
4b	11 ± 0.5	8 ± 0.20	7 ± 0.4	8 ± 0.15
4c	8 ± 0.09	10 ± 0.11	9 ± 0.005	11 ± 0.38
4d	14 ± 0.15	8 ± 0.2	15 ± 0.10	11 ± 0.11
4e	10 ± 0.11	20 ± 0.1	11 ± 0.15	17 ± 0.2
4f	10 ± 0.25	15 ± 0.2	21 ± 0.15	20 ± 0.15
4g	23 ± 0.04	16 ± 0.40	15 ± 0.56	18 ± 0.15
4h	21 ± 0.13	17 ± 0.03	12 ± 0.39	19 ± 0.11
4i	19 ± 0.17	12 ± 0.15	0	14 ± 0.2
4j	11 ± 0.23	10 ± 0.07	12 ± 01	10 ± 0.32
5a	5.6 ± 0.52	20 ± 0.2	8 ± 0.25	4 ± 0.2
5b	10 ± 0.11	12 ± 0.12	9 ± 0.15	5 ± 0.3
5c	16 ± 0.16	10 ± 0.09	12 ± 0.17	18 ± 0.60
5d	22 ± 0.1	23 ± 0.05	26 ± 0.1	12 ± 0.005
5e	20 ± 0.15	24 ± 0.06	13 ± 0.46	15 ± 0.3
5f	12 ± 0.11	24 ± 0.15	10 ± 0.11	18 ± 0.10
5g	11 ± 0.07	20 ± 0.06	14 ± 0.11	9 ± 0.06
5h	20 ± 0.16	21 ± 0.1	16 ± 0.3	10 ± 0.1
5i	15 ± 0.16	10 ± 0.10	19 ± 0.12	11 ± 0.04
5j	17 ± 0.18	12 ± 0.43	10 ± 0.04	20 ± 0.064

Values are Mean of triplicates; Standard 10 mg/disc

CONCLUSION

In summary, we successfully synthesized new 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives as antibacterial molecules. The synthesis of the chalcone derivatives were involved by Claisen-Schmidt reaction of 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone with substituted benzaldehydes in the presence of 30% methanoic NaOH and water. Generally, chalcones are considered to be useful intermediates in several cyclisation reactions to produce heterocyclic compounds of diverse biological importance. Finally, new 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives were synthesized by the cyclization of compounds (3a–j) with hydroxylamine hydrochloride and phenyl hydrazine in absolute ethanol. Some of 1,4-benzodioxinylisoxazole and 1,4-benzodioxinylpyrazole derivatives exhibited excellent antibacterial effect but some of the synthesized compounds showed only moderate effect. It was assumed that the synthetic pathway and antibacterial study will provide a framework for the further design and development of potent and selective heterocyclic compounds.

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