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Synthesis of 2-(oxadiazolo, pyrimido, imidazolo, and benzimidazolo) substituted analogues of 1,4-benzodiazepin-5-carboxamides linked through a phenoxyl bridge

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Abstract. Exceedingly facile single-step expedient protocols based on the versatility and reactivity of corresponding intermediates amidine and imidate (**8** and **9**), derived from 5-carboxamido-1,4-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide have been developed to provide an easy installation of the oxadiazole, pyrimidine, imidazole and benzimidazole **(9–14)** based privileged templates at 2-position of 5-carboxamido-1,4-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide **(4)**, through a phenoxyl spacer, by utilizing the synthetic strategy depicted in schemes 1 and 2.

Keywords. 1,4-benzodiazepine; oxadiazole; pyrimidine; imidazole; benzimidazole; amidine and imidate ester.

1. Introduction

Recently, the privileged[1] molecular framework of benzodiazepines has been actively studied in view of their ability to provide ligands to a number of functionally and structurally discrete biological receptors.[2–5] The advent of anti-human immunodeficiency virus (HIV) activity in 1,4-benzodiazepine and imidazole derivative TIBO[6] (a) (tetrahydroimidazobenzodiazepinone), the dipyrido diazepine derivative (nevirapine)[7] (b), pyrimidine derivative (etravirine)[8] (c) and oxadiazole derivative (raltegravir)[9] (d) (figure 1) prompted us to explore the possibility of developing some such analogues of 1,4-benzodiazepines which contained in its nucleus the vital fragments of oxadiazole,[10] pyrimidine,[11] imidazole,[12] and benzimidazole[13] scaffold on the premise that their presence in tandem with the same molecular framework could contribute significantly to provide a beneficial effect on the overall biological efficacy in the resulting molecules.

To create the novel heterocyclic scaffolds of biological interest through the simple and straightforward expedient routes, we explored the amidine[14] **(8)** and imidate ester[15] **(9)** based cyclization reactions for the incorporation of the oxadiazole, pyrimidine, imidazole and benzimidazole based privileged template on the 2-position of 1,4-benzodiazepine nucleus **(3)** through a phenylamino spacer (schemes 1 and 2).

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2. Experimental

2.1 *General procedures*

All the melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 infrared. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400 MHz spectrometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1).

N-chloroacetylisatin **(2)** (M.p. 210–11°C) and methyl-1,3-dihydro-2*H*-[1,4]-benzodiazepin-2-one-5-carboxylate **(3)** (M.p. 173–75°C) were prepared according to the reported procedure for their preparation in the literature.[23–26]

2.2 *Preparation of 1,3-dihydro-[2H]-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (**4**)*

Methyl-1,3-dihydro-[*2H*]-[1,4]-benzodiazepin-2-one-5-carboxylate **(3)** (10.9 g, 0.05 mol) and *N*-methyl piperazine (5.0 g, 0.05 mol) were taken in ethanol (100 mL). The reaction mixture was refluxed for 12 h on the water bath. The completion of the reaction was checked by TLC. The mixture was cooled and poured

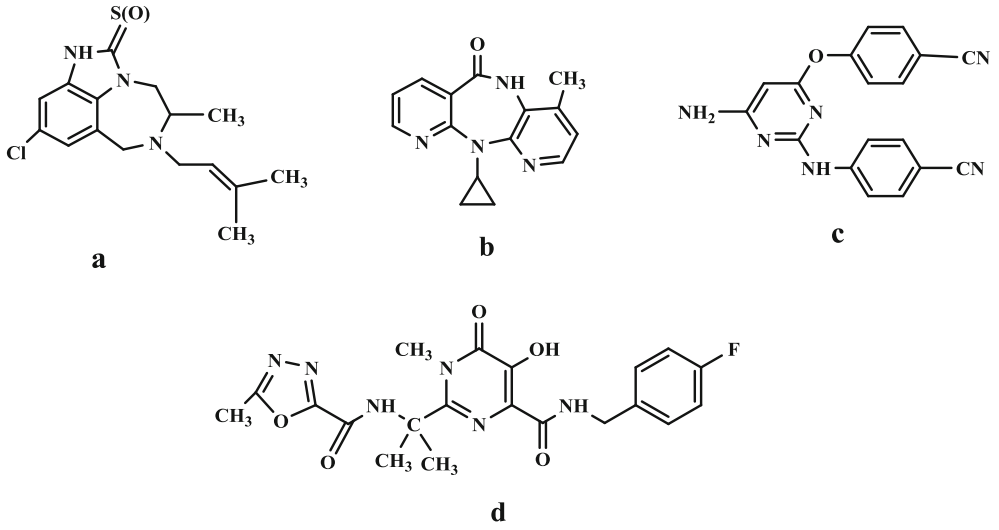
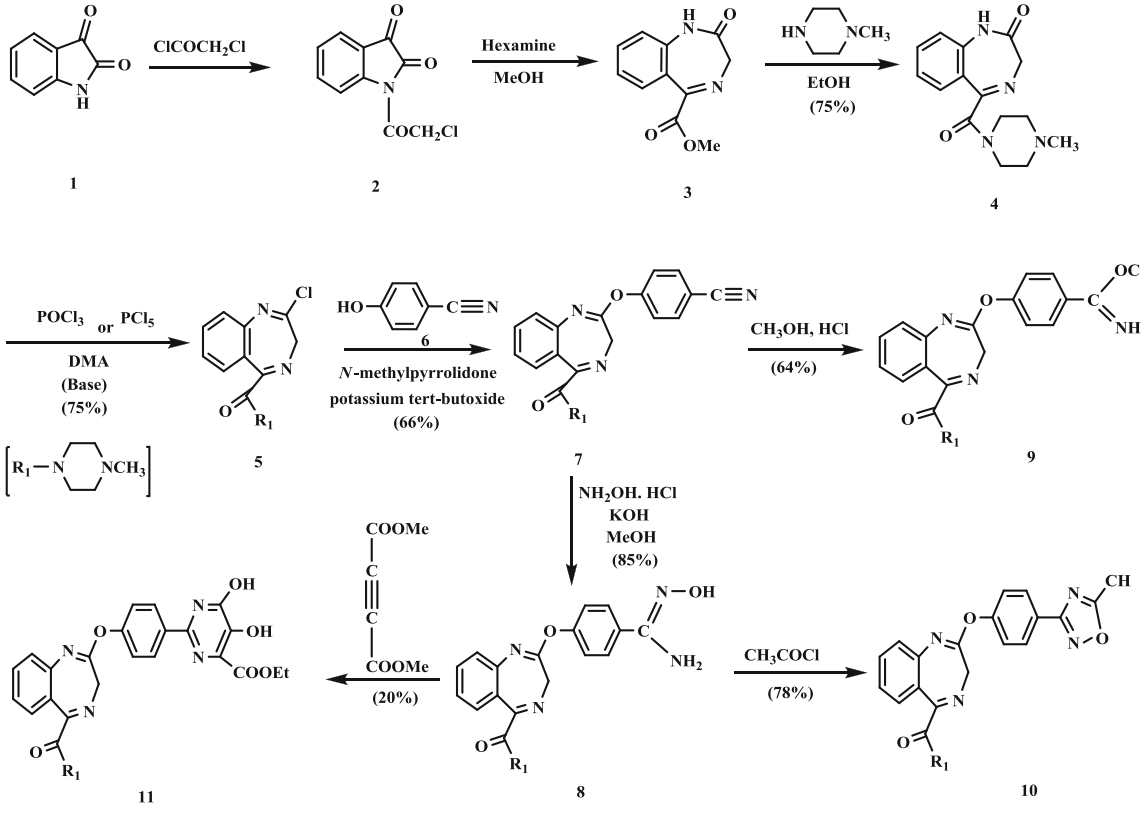
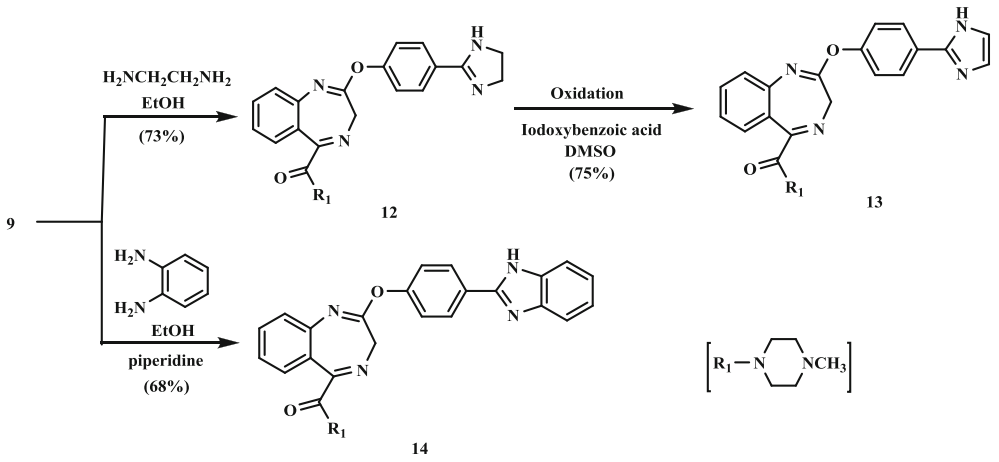


Figure 1. Structures of TIBO (**a**), (nevirapine) (**b**), (etravirine) (**c**) and (raltegravir).

on crushed ice, the resulting solid was filtered, washed with dilute ethanol, dried and recrystallized from ethanol-chloroform mixture (1:9), to give compound **4** (12.37 g, 75%, M.p. 257–258°C). IR (KBr) cm^{-1}: 3330 (NH str.), 2950 (C-H str. ArH), 1675 (C=O str.), 1660 (C=C str. ArH), 1590 (C=N str.), 1580 (NH bending), 1430 (C-H bending, CH_3), 1140 (C-N str.); ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm: 8.0 (s, 1H), 7.27–7.86 (m, 4H), 3.60 (s, 2H), 3.20 (t, J = 7.4 Hz, 4H), 2.27 (t, J = 7.2 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$)δ ppm: 45.2 (CH_3), 47.3 (CH_2, diazepine), 49.5, 82.3 (CH_2, piperazine), 113.0, 117.7 (C, arene), 125.4, 116.7 (C, arene), 128.2, 126.5 (CH, arene), 149.5, 158.2 (C=N), 164.5 (C=O); MS: [M^+]: 286, Anal.



Scheme 1. Synthesis of oxadiazole and pyrimidine bearing benzodiazepine nucleus.



Scheme 2. Synthesis of imidazole and benzimidazole bearing benzodiazepine nucleus.

calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 62.75; H, 6.32; N, 19.48.

2.3 *Preparation of 2-chloro-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (**5**)*

A solution of compound **4** (10 g, 0.06 mol), $POCl_3$ (5 mL, 0.06 mol), *N*, *N*-dimethylaniline (14 mL, 0.1 mol), and benzene (100 mL) were refluxed for 7 h and allowed to cool overnight. The cold reaction mixture was poured in ice water (100 mL) and stirred for 30 min. until the reaction mixture reached room temperature. It was then extracted with ether and the solvent layer was washed with water and brine, dried (over anhydrous $MgSO_4$), filtered and evaporated. Trituration with ether gave compound **5** (8.0 g, 75%, M.p. 120–122°C). IR (KBr) cm^{-1}: 2955 (C-H str. ArH), 1680 (C=O str.), 1590 (C=C str. ArH), 1570 (C=N str.), 1435 (C-H bending, CH_3), 1140 (C-N str.), 710 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm: 7.33–7.83 (m, 4H), 3.60 (s, 2H), 3.20 (t, J = 7.4 Hz, 4H), 2.27 (t, J = 7.5 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$)δ ppm: 45.2 (CH_3), 46.0 (CH_2, diazepine), 47.8, 95.3 (CH_2, piperazine), 114.6, 118.8 (C, arene), 126.5, 128.2 (CH, arene), 148.6, 155.1, (C=N) 158.3 (C-Cl), 164.6 (C=O); MS: [M^+]: 304, Anal. calcd. for $C_{15}H_{17}ClN_4O$: C, 59.24; H, 5.65; N, 18.34. Found: C, 59.11; H, 5.67; N, 18.28.

2.4 *Preparation of 2-[4'-cyanophenoxyl-[1,4]-benzodiazepin-5-(-4"-methylpiperazinyl)]-carboxamide (**7**)*

To a solution of compound **5** (1.50 g, 0.01 mol) and 4-hydroxybenzonitrile **(6)** (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 mL) at 0–5°C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 6 h. The reaction was allowed to reach to room temperature and then cold water (300 mL) was added. The reaction mixture was filtered; the residue was suspended in water (150 mL) and acidified to pH 6–7 using conc. HCl. The product was filtered and washed with 15 mL of water. It was extracted by ethyl acetate (2 × 50 mL). The product obtained on evaporation of solvent was washed with 5 mL of chilled ethyl acetate. It was finally dried at 55–60°C under vacuum to give compound **7** (1.26 g, 66%, M.p. 297–298.5°C). IR (KBr) cm^{-1}: 2980 (C-H str. ArH), 2225 (CN str.), 1685 (C=O str.), 1590 (C=C str. ArH), 1525 (C=N str.), 1470 (C-H bending, CH_3), 1250 (C-O str.), 1035 (C-N str.); ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm: 7.33–7.81 (m, 4H), 3.6 (s, 2H), 3.20 (t, J = 7.5 Hz, 4H), 2.27 (t, J = 7.6 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 42.1 (CH_3), 44.3 (CH_2, diazepine), 45.6, 58.5 (CH_2, piperazine), 106.0 (C-CN, cyanophenoxyl), 116.4 (CH, cyanophenoxyl), 117.8, 148.4 (C, arene), 118.1 (CN), 127.5, 131.2 (CH, arene), 134.1 (CH, cyanophenoxyl), 164.5 (C-O, cyanophenoxyl), 165.7 (C=N), 200.1 (C=O); MS: [M^+]: 387, Anal. Calcd. for $C_{23}H_{24}N_5O_2$: C, 68.64; H, 6.01; N, 17.40; Found: C, 68.47; H, 5.99; N, 17.35.

2.5 *Preparation of 5-oxo-[(benzo-[1,4]-diazepin-2-yloxy)-carboximidamide-5-(-4"-methylpiperazinyl)]-carboxamide (**8**)*

Hydroxylamine hydrochloride (1 g, 0.01 mol) in methanol (10 mL) was added to an equimolar stirred solution of potassium hydroxide in methanol (10 mL). The mixture was stirred for 15 min and the precipitated potassium chloride was removed by filtration. The

filtrate was added to an equimolar amount of the above nitrile **(7)** (3.87 g, mol), and the solution was stirred overnight at 40°C, then cooled to room temperature and concentrated. The resulting residue was triturated with water giving, after drying under vacuum, a white solid consisting mainly of the title product **8**, (3.56 g, 85%, M.p. 181–83°C). IR (KBr) cm^{-1}: 2600–3510 [broad OH str. (oxime)], 3310 [NH str. (NH_2 group)], 2855 (C-H str. ArH), 1690 (C=O), 1635 (NH bending), 1615 (C=C str.), 1580 (C=N str.), 1530 (C=C str. ArH), 1480 (C-H bending CH_3), 1170 (C-N str.), 1080 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33–7.78 (m, 4H), 7.19 (s, 2H), 7.09–7.41 (m, 4H), 3.6 (s, 2H), 3.20 (t, $J = 7.5$ Hz, 4H), 2.28 (t, $J = 7.6$ Hz, 4H), 2.25 (s, 3H), 2.33 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 13.2 (C=N-OH), 45.4 (CH_3), 47.5 (CH_2, diazepine), 49.1, 118.0 (CH_2, piperazine), 127.6, 129.8 (CH, phenoxyl), 135.5, 138.7, 146.6, 147.8 (CH, arene), 143.3, 149.5 (C, arene), 134.0, 153.4 (C, phenoxyl), 157.6 (C=O), 159.8 (C-O), 164.5 (C=N); MS: [M^+]: 420, Anal. Calcd. for $C_{22}H_{24}N_6O_3$: C, 62.84; H, 5.75; N, 19.99; Found: C, 62.91; H, 5.76; N, 19.94.

2.6 *Preparation of 5-oxo-[(benzo-[1,4]-diazepin-2-yloxy)-ethylimidate-5-(-4”-methylpiperazinyl)]-carboxamide (**9**)*

The compound **7** (3.87 g, 0.01 mol) was dissolved in absolute ethanol (10 mL) and stirred for 15 min with ice-bath cooling. Then the imidate hydrochloride **(9)** was prepared by passing HCl gas through the above solution. HCl gas was passed for 7 h with constant stirring at room temperature. The completion of the reaction was checked by TLC, after completion the precipitation of reaction mixture was done by adding diethyl ether to it, filtered, dried over vacuum, and recrystallized from petroleum ether to yield compound **9**, (2.68 g, 64%, M.p. 81–83°C). IR (KBr) cm^{-1}: 3350 (NH str.), 2950 (C-H str. ArH), 1670 (free C=O str.), 1590 (NH bending), 1595–1610 (C=N str.), 1555 (C=C str. ArH), 1440 (C-H bending CH_3), 1160 (C-N str.), 1140 (C-O str.), 1070 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33–7.83 (m, 4H), 6.35–7.20 (m, 4H), 3.7 (s, 1H), 3.6 (s, 2H), 3.40 (s, 3H), 3.21 (t, $J = 7.4$ Hz, 4H), 2.27 (t, $J = 7.5$ Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2 (CH_3), 47.4 (CH_2, diazepine), 48.2, 116.6 (CH_2, piperazine), 128.1, 127.0 (CH, phenoxyl), 135.2, 129.3, 130.9, 132.8 (CH, arene), 148.1, 158.3 (C, arene), 134.1, 154.1 (C, phenoxyl), 156.6 (C=O), 164.3 (C-O), 174.5 (C=N); MS: [M^+]: 419, Anal. Calcd. for $C_{23}H_{25}N_5O_3$: C, 65.85; H, 6.01; N, 16.70; Found: C, 65.69; H, 5.98; N, 16.65.

2.7 *Preparation of 2-[4-(5-methyl-1,2,4-oxadiazol-3-phenoxyl)-[1,4]-benzodiazepin-5-(4”-methyl-piperazinyl)]-carboxamide (**10**)*

Compound **8** (2.10 g, 0.005 mol) was refluxed in acetyl chloride (10 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol gave the product **10**, (1.734 g, 78%, M.p. 118–20°C). IR (KBr) cm^{-1}: 2880 (C-H str. ArH), 1680 (C=O), 1610 (C=C str.), 1580 (C=N str.), 1535 (C=C str. ArH), 1430 (C-H bending CH_3), 1180 (C-N str.), 1090 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33–7.78 (m, 4H), 6.81–7.91 (m, 4H), 3.6 (s, 2H), 3.20 (t, $J = 7.3$ Hz, 4H), 2.60 (s, 3H), 2.28 (t, $J = 7.4$ Hz, 4H), 2.25 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 12.4 (CH_3, oxadiazole), 44.0 (CH_3), 45.8 (CH_2, diazepine), 47.2, 49.4 (CH_2, piperazine), 117.5, 127.4 (CH, phenoxyl), 131.6, 135.8, 138.1 (CH, arene), 143.3, 146.5 (C, arene), 134.7, 153.5 (C, phenoxyl), 158.7 (C=O), 157.0 (C-O), 164.6 (C=N), 168.4, 175.1 (2C, oxadiazole); MS: [M^+]: 444, Anal. Calcd. for $C_{24}H_{24}N_6O_3$: C, 64.85; H, 5.44; N, 18.91; Found: C, 64.68; H, 5.43; N, 18.96.

2.8 *Preparation of 2-[4’-(4”-ethylcarboxylate-5”,6”-dihydroxypyrimidin-2”-yl)phenoxyl-[1,4]-benzo-diazepin-5-(4”’-methyl-piperazinyl)-carboxamide (11) Compound **8***

(2.94 g, 0.007 mol) was suspended in chloroform (20 mL) and refluxed overnight in the presence of 1.0 equiv of dimethyl acetylenedicarboxylate (0.87 mL). After being cooled to room temperature, volatiles were evaporated and the residue was refluxed in xylene (25 mL) for 3 h. The mixture was cooled to room temperature to allow the formation of precipitate of compound **11**, was collected by filtration and washed with diethyl ether, (0.645 g, 20%, 125–27°C). IR (KBr) cm^{-1}: 3480–3500 (OH str.), 3010 (C-H str. ArH), 1685 (C=O str.), 1740 (C=O str. ester), 1640 (C=N str.), 1610 (C=C unsaturated), 1580 (C=C str. ArH), 1460 (C-H bending CH_3), 1190 (C-N str.), 1150–1200 (ester group), 1090–1105 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 12.20 (s, 1H), 7.33–7.83 (m, 4H), 6.83-7.80 (m, 4H), 5.35 (s, 1H), 3.6 (s, 2H), 4.30 (q, $J = 7.3$ Hz, 2H), 1.29 (t, $J = 7.4$ Hz, 3H), 3.20 (t, $J = 7.5$ Hz, 4H), 2.27 (t, $J = 7.6$ Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 16.1 (CH_3, ester), 45.2 (CH_3), 47.0 (CH_2, diazepine), 48.9, 49.9 (CH_2, piperazine), 72.1 (CH_2, ester), 116.6, 130.3 (CH, phenoxyl), 127.5, 155.8 (C, phenoxyl), 126.3, 130.6 (CH, arene), 132.8, 148.2 (C, arene), 143.1, 145.4, 163.1 (C, pyrimidine), 149.8 (C-OH, pyrimidine), 158.1 (C=O),

164.3 (C=N, C-O), 168.1 (C=O, ester); MS: [M^+]: 544, Anal. Calcd. for $C_{28}H_{28}N_6O_6$: C, 61.76; H, 5.16; N, 15.43; Found: C, 61.58; H, 5.14; N, 15.38.

2.9 *Preparation of 2-[4'-(dihydroimidazol-2"-yl)phenoxyl-[1,4]-benzodiazepin-5-(4"-methyl-piperazinyl)]-carboxamide (**12**)*

A mixture ethylenediamine (1.08 g, 0.01 mol), imidate ester **(9)** (0.586 g, 0.0014 mol) and ethanol (15 mL) was refluxed for 11 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate to give compound **12**, (0.44 g, 73%, M.p. 136–37°C).

2.10 *Preparation of 2-[4'-(imidazol-2"-yl)phenoxyl-[1,4]-benzodiazepin-5-(4"-methyl-piperazinyl)]-carboxamide (13) via oxidation of compound **12***

Iodoxybenzoic acid (0.4 g, 1.53 mmol) was added as a solid to a solution of compound **12** (0.0015 mol) in DMSO (1 mL) and stirred at 45°C for 11 h. The mixture was cooled to room temperature and quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and then basified with saturated aqueous $NaHCO_3$ (1 mL). Following extraction with EtOAc (15 mL), the organic phase was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to yield the desired product **13**, (0.481 g, 75%, M.p. 130–32°C). IR (KBr) cm^{-1}: 3320 (NH str. imidazole ring), 2970 (C-H str. ArH), 1680 (C=O), 1680 (C=C unsaturated), 1625 (C=N str.), 1590 (NH bending), 1550 (C=C str. ArH), 1460 (C-H bending CH_3), 1050 (C-N str.), 1040 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm: 13.4 (s, 1H), 7.33–7.83 (m, 4H), 7.02 (d, J = 7.8 Hz, 2H), 6.81–7.90 (m, 4H), 3.6 (s, 2H), 3.21 (t, J = 7.4 Hz, 4H), 2.27 (t, J = 7.3 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$)δ ppm: 45.2 (CH_3), 47.1 (CH_2, diazepine), 48.8 (CH_2, piperazine), 116.1, 127.1 (CH, phenoxyl), 122.5 (CH, imidazole), 126.5, 132.2 (CH, arene), 130.3, 147.3 (C, arene), 132.5, 155.3 (C, phenoxyl), 148.7 (C, imidazole), 158.1 (C=O), 164.4 (C=N, C-O); MS: [M^+]: 428, Anal. Calcd. for $C_{24}H_{24}N_6O$: C, 67.27; H, 5.65; N, 19.61; Found: C, 67.11; H, 5.63; N, 19.53.

2.11 *Preparation of 2-[4'-(benzimidazol-2"-yl)phenoxyl-[1,4]-benzodiazepin-5-(4"-methyl-piperazinyl)]-carboxamide (**14**)*

To a solution of imidate ester **(9)** (1.257 g, 0.003 mol) in ethanol (10 mL) was added 2–3 drops of piperidine and *o*-phenylenediamine (1.08 g, 0.01 mol). The mixture was heated under reflux for 11 h and then 1 mL of AcOH was added. The refluxing was continued for 1 h. About half of the solvent was distilled off and the resulting mixture was allowed to stand at room temperature. The crystalline compound **14** thus separated was filtered, washed with 5 mL of cold aq. ethanol (50:50 by v/v) and dried, (0.975 g, 68%, M.p. 177–79°C). IR (KBr) cm^{-1}: 3370 (NH str. benzimidazole ring), 3010 (C-H str. ArH), 1670 (free C=O str.), 1610 (C=C str. ArH), 1595 (C=N str.), 1560 (NH bending), 1440 (C-H bending CH_3), 1150 (C- N str.), 1110 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm: 7.33–7.83 (m, 4H), 7.22–7.59 (m, 4H), 6.81–7.91 (m, 4H), 5.0 (s, 1H), 3.6 (s, 2H), 3.21 (t, J = 7.5 Hz, 4H), 2.27 (t, J = 7.6 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$)δ ppm: 45.1 (CH_3), 47.0 (CH_2, diazepine) 48.9 (CH_2, piperazine), 113.2, 155.0 (C, phenoxyl), 115.9, 122.1 (CH, benzimidazole), 116.2, 127.3 (CH, phenoxyl), 126.8, 132.7 (CH, arene), 130.0, 148.1 (C, arene), 142.3 (C, benzimidazole), 152.4 (C=N, benzimidazole), 158.7 (C=O), 164.2 (C=N, C-O); MS: [M^+]: 478, Anal. Calcd. for $C_{28}H_{26}N_6O_2$: C, 70.28; H, 5.48; N, 17.56; Found: C, 70.16; H, 5.50; N, 17.61.

2.12 *Biological studies*

Condensed heterocyclic systems containing oxadiazole, pyrimidine, imidazole, and benzimidazole and 1,4-benzodiazepines have attracted the attention of chemists owing to these nuclei having been identified in the literature as the most active pharmacophores in drug design and synthesis. It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological profiles of that molecule. All the compounds were screened for their anti-microbial activity by disc diffusion method at 100 μg/mL concentration in DMF against *Pseudomonas aeruginosa* **(MTCC 1688)** and *Bacillus cerus* **(MTCC 1305)** and anti-fungal activity against *Macrophomina phaseolina* **(MTCC 166)** and *Fusarium solani* **(MTCC 350)**. The zone of inhibition and activity index were determined in comparison of the standard drugs 'Streptomyacin' and 'fluconazol'. The outcome of this study is presented in tabular form in table 1. All these compounds were found to be active against the bacterial and fungal strains.

3. Results and Discussion

Ubiquity of 1,4-benzodiazepine nucleus in chemical literature is undoubtedly a consequence of multifarious

Table 1. Anti-bacterial and antifungal activity of compounds **7-14**.

Comp. No.	*Pseudomonas aeruginosa*		*Bacillus cerus*		*Macrophomina phaseolina*		*Fusarium solani*	
	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard
Streptomycin (std. Antibacterial)	25	100	24	100	–	–	–	–
Flucanazol (std. Anti-fungal)	–	–	–	–	26	100	26	100
7	18	72.0	23	95.8	24	92.3	20.3	78.0
8	22	88.0	22	91.6	21.3	81.9	15.1	58.0
9	15	60.0	21	87.5	24	92.3	12.3	47.3
10	15.1	60.4	18	75.0	24.5	94.2	13.2	50.7
11	24	96.0	19	79.1	25	96.1	15.0	57.6
13	23	92.0	22.5	93.7	23	88.4	23.6	90.7
14	24.5	98.0	20	83.3	22	84.6	20.2	77.6

biological response which they elicit in combating a variety of body ailments. Recent demonstrations that some of their derivatives can be used as privileged templates in the development of potential agents for the treatment of Acquired Immunodeficiency Syndrome (AIDS)[16] has stimulated further interest in this nucleus from yet another perspective. As a part of our endeavour to create novel heterocyclic scaffolds of anticipated biological activity from easily accessible starting materials, here in this paper we report, the preliminary results of our studies on the synthesis of oxadiazole, pyrimidine, imidazole, and benzimidazole incorporated 1,4-benzodiazepines linked to it through a 2-*p*-phenoxyl spacer in **10–14**. Compound **(7)** was obtained through a five step strategy on isatin **(1)**. The first step of this strategy involved the conversion of *N*-chloroacetylisatin **(2)** to 1,4-benzodiazepine-2-one-5-carboxylate **(3)**, using a literature procedure.[17–20] In view of the medicinal importance of piperazine derivatives, it was considered of interest to append this nucleus on to the 5-methoxycarbonyl function to form the 5-carboxamido substituted derivatives (**4**), which in the subsequent step was treated with $POCl_3$[21] in dimethylaniline (DMA) to afford the corresponding 2-chloro derivative **(5)**. The 2-Cl atom (an imino chloride/imidoyl chloride) is a highly reactive species known to be activated for nucleophillic attack. Its nucleophillic displacement with *p*-hydroxybenzonitrile **(6)** yielded compound **7** (scheme 1).[22–24] A perusal of literature[25] on the potential of amidines and imidate ester intermediates for their use as versatile precursors in synthesis, has demonstrated that these were readily formed from the reaction of compound **7** with H_2N-OH.HCl + KOH (in MeOH) following the procedure reported in the literature[26] for such reactions on substrates containing the nitrile group. Established protocols on amidine derivative **(8)** was applied, employing the reagents acetyl chloride and dimethylacetylene dicarboxylate to form the compounds **(10)** (oxadiazole bearing) and **(11)** (pyrimidine bearing) benzodiazepine nucleus respectively (scheme 1). The second key intermediate was **(9)** formed from the reaction of compound **7** with R-OH + HCl. Established protocols on imidate derivative **(9)** was applied, employing the reagents ethylenediamine and *o*-phenylenediamine to form the dihydroimidazole **(12)** [whose oxidation with iodoxybenzoic acid provided imidazole **(13)**] and benzimidazole **(14)** bearing benzodiazepine nucleus, respectively (scheme 2).[27–30] All the synthesized compounds gave satisfactory results of their microanalysis, IR, ^{1}H NMR, ^{13}C NMR and MS spectral data which were found to be consistent to the assigned structures.

4. Conclusion

In conclusion, two elegant protocols have been developed to provide an easy access to the biologically active novel oxadiazole, pyrimidine, imidazole and benzimidazole incorporated analogues of 1,4-benzodiazepine derivatives linked to it by a phenoxyl spacer, utilizing the potential of corresponding amidine **(8)** and imidate **(9)** intermediates in high yield and purity. The formulated plan provided an easy incorporation of the vital fragments of the biologically active nuclei and the anti-HIV prone 1,4-benzodiazepine nuclei together, in

the same molecular framework in acceptable yield and purity, for the evaluation of their bio-efficiency over the existing potential antimicrobial agents.

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR spectra, mass spectra, analytical reports and representative photographs of the zone of inhibition is provided in the supporting information at www.ias.ac.in/chemsci.

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