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Synthesis of Some 1,5-Benzodiazepine Derivatives as a New Class of Antimicrobial Agents

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A series of ceric ammonium nitrate promoted 1,5-benzodiazapine derivatives (**A-K**) were synthesised and characterized by IR, $^{1}H/^{13}C$ NMR, mass and elemental analysis. The *in vitro* antibacterial and antifungal activities of the compounds were evaluated by paper disc diffusion method. The minimum inhibitory concentration (MIC) of the compounds was also determined by agar streak dilution method. Compound **E** was found to exhibit the most potent *in vitro* antimicrobial activity with MIC of 1.2, 1.2, 1.3, 1.2, 3.2 and >100 µg mL^{-1} against *B. subtilis*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa*, *Candida albicans*.

Key Words: 1,5-Benzodiazepines, Ceric ammonium nitrate, Antimicrobial activitiy.

INTRODUCTION

The 1,5-benzodiazepine derivatives, due to their accessibility, easy functionalization and potential pharmacological properties have received significant attention and the core is indeed a 'privileged scaffold' found in compounds active against a variety of target types including peptide hormones (such as CCK)[1a], interleukin converting enzymes (ICE)[2] and potassium blockers (Ik)[3]. More recently, the area of biological interest of 1,5-benzodiazepines has been extended to various diseases such as cancer[4], viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase),[5] cardiovascular disorders[6,7]. In addition, some 1,5-benzodiazepines show antidepressive, antifungal, antibacterial, antifeedant, antiinflammatory, analgesic and anticonvulsant properties[8-10].

Despite of their importance from pharmacological and industrial point of view, only a few methods of preparation were reported in the literature. Recently, the authors have reported the synthesis of 1,5-benzodiazepine derivatives using ceric ammonium nitrate (CAN)[11]. In continuation of the

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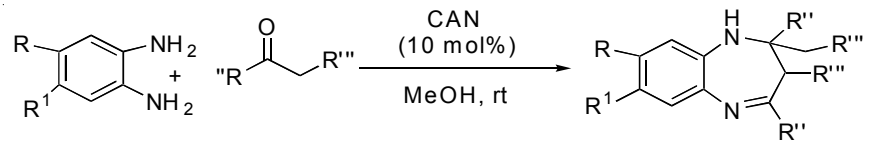
work, recent efforts have been made to develop new synthetic routes for carbon-carbon and carbon-heteroatom bond formation and biologically relevant heterocycles[12-15]. We have synthesized various structurally divergent 1,5-benzodiazepines derivatives and screened them for antibacterial and antifungal activities and the results are presented herein.

In the present study, substituted *o*-phenylenediamines (*o*-PDs', 1 equiv.) were reacted with substituted acetophenones (2.2 equiv.) using CAN (10 mol %) in methanol while stirring at room temperature to obtain the corresponding 1,5-benzodiazepines.



R,R^1=H; R=CH_3, R=H;
R=Cl, R'=H; R=NO_2, R'=H;
R=CH_3, R^1=CH_3; R=Cl, R^1=Cl;

(11 compounds)

Scheme-I

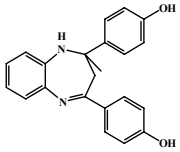
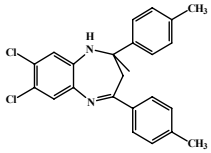
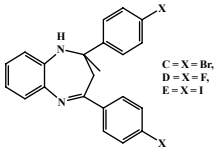
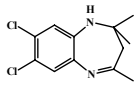
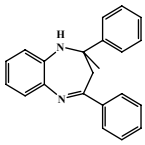
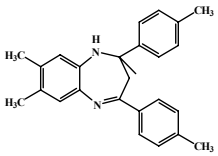
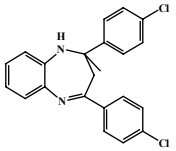
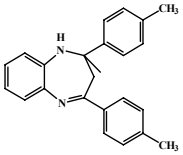
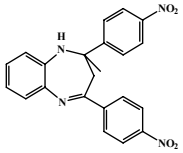
Biological investigation: The *in vitro* antibacterial (*B. subtilis* MTCC 1133, *P. vulgaris* MTCC 1771, *K. pneumoniae* MTCC 2405, *P. aeruginosa* MTCC 1036) and antifungal (*Candida albicans* ATCC 2091 and *Aspergillus niger* ATCC 9029) activities of the compounds were evaluated by paper disc diffusion method and the MIC (minimum inhibitory concentration) was determined by agar streak dilution method.

EXPERIMENTAL

Melting points have been recorded on an electrothermal melting point apparatus. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB104 with KBr pellets. ^{1}H NMR spectra were recorded on 300 MHz-Bruker DPX 200. The chemical shifts are reported as parts per million downfield from tetramethyl silane. Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were performed in Heraeus CHN Rapid Analyzer. All the compounds gave satisfactory chemical analyses (± 0.4 %). The purity of the compounds was checked by TLC on precoated SiO_2 gel (HF254, 200 mesh) aluminum plates (E. Merck) using *n*-hexane: ethyl acetate (8:2) as mobile phase and visualized by iodine vapours.

General method of synthesis of 1,5-BDPs' (Compounds A-K): A mixture of *o*-phenylenediamine (1.0 mmol), ketone (2.2 mmol) and CAN (0.055 g, 10 mol %) in MeOH (2 mL) was stirred at room temperature for the time specified in Table-1. After the reaction was over, it was diluted

TABLE-1
CAN-PROMOTED SYNTHESIS OF 1,5-BENZODIAZEPINES

Compound	Benzodiazepine	Time (h)	Yields (%)[a]
A		5.0	85
B		4.0	90
C	 C = X = Br, D = X = F, E = X = I	6.0	74
D		3.5	95
E		4.5	88
F		3.0	90
G		3.5	89
H		4.5	76
I		4.0	92
J		4.0	87
K		4.5	80

[a]Yields refer to the isolated pure products after column chromatography.

with H_2O and extracted with Et_2O (3 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel to afford the corresponding pure 1,5-benzodiazapine.

Spectral data

4-[4-(4-Hydroxyphenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-yl]phenol (Entry A): Yellow crystalline solid, m.p. 219-220ºC; IR (KBr, ν_{max}, cm^{-1}): 3339, 1636, 1599; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 2.77 (d, 1H, *J* = 12.63 Hz), 2.89 (d, 1H, *J* = 7.43 Hz), 4.18 (br s, 1NH), 6.57-6.64 (m, 4H), 6.81-7.00 (m, 2H), 7.10-7.18 (m, 2H), 7.28-7.55 (m, 4H); MS (EI): m/z = 344 (M^+); Anal. Calcd. (%) for $C_{22}H_{20}N_2O_2$: C 76.74, H 5.81, N 8.15; found (%): C 76.76, H 5.84, N 8.13.

7,8-Dichloro-2-methyl-2,4-di(4-methylphenyl)-2,3-dihydro-1H-1,5-benzodiazepine (Entry B): Pale yellow solid, m.p. 179-180ºC; IR (KBr, ν_{max}, cm^{-1}): 3434, 1636, 1597, 817; ^1H NMR (300 MHz, $CDCl_3$): δ =1.75 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 2.95 (d, 1H, *J* = 13.60 Hz), 3.09 (d, 1H, *J* = 13.60 Hz), 3.50 (br s, 1NH), 6.88 (s, 1H), 7.05-7.09 (t, 3H), 7.28 (s, 1H), 7.38-7.44 (t, 3H), 7.50-7.53 (d, 2H); MS (EI): m/z= 409 (M^+); Anal. Calcd. (%) for $C_{24}H_{22}N_2Cl_2$: C 70.42, H 5.42, N 6.85; found (%): C 70.35, H 5.60, N 6.88.

2,4-Di(4-bromophenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry C): Brown solid, m.p. 102-104ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 1640, 1589, 574; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.87 (d, 1H, *J* = 12.84 Hz), 3.00 (d, 1H, *J* = 13.60 Hz), 2.65 (br s, 1NH), 6.98 (m, 1H), 7.00 (m, 6H), 7.22 (m, 1H), 7.47 (m, 4H); MS (FAB): m/z = 471 (M^++1); Anal. Calcd. (%) for $C_{22}H_{18}N_2Br_2$: C 56.17, H 3.82, N 5.95; found (%): C 56.19, H 3.78, N 5.89.

2,4-di(4-fluorophenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry D): Pale yellow crystalline solid, m.p. 104-105ºC; IR (KBr, ν_{max}, cm^{-1}): ν 3271, 1651, 1603, 1231; ^1H NMR (300 MHz, $CDCl_3$): δ =1.75 (s, 3H), 2.87 (d, 1H, *J* = 13.60Hz), 3.04 (d, 1H, *J* = 12.84 Hz), 3.30 (br s, 1NH), 6.75-6.79 (m, 1H), 6.82-6.92 (m, 4H), 7.00-7.05 (m, 2H), 7.19-7.25 (m, 1H), 7.48-7.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.72, 42.94, 73.38, 114.70, 114.79, 114.97, 115.06, 126.22, 127.0, 128.50, 129.20, 135.46, 137.44, 140.36, 143.2, 160.23, 162.22, 165.26, 165.53, 163.50; MS (EI): m/z = 348 (M^+); Anal. Calcd. (%) for $C_{22}H_{18}N_2F_2$: C 75.86, H 5.17, N 8.04; found (%): C 75.82, H 5.20, N 8.07.

2,4-Di(4-iodophenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry E): Pale yellow crystalline solid, m.p.143-144ºC; IR (KBr, ν_{max}, cm^{-1}): 3259, 1636, 1579, 462; ^1H NMR (200 MHz, $CDCl_3$): δ =1.71 (s, 3H), 2.85 (d, 1H, *J* = 13.60 Hz), 2.99 (d, 1H, *J* = 12.84 Hz), 3.32 (br s, 1NH), 6.73-6.75 (m, 1H), 6.98-7.03 (m, 2H), 7.21-7.33 (m, 5H), 7.53-7.58

(m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.26, 43.37, 74.10, 93.38, 97.40, 122.07, 122.56, 127.28, 128.24, 129.23,129.28, 137.84, 137.98, 139.40, 140.39, 147.64, 166.81; MS (FAB): m/z = 565 (M^++1); Anal. Calcd. (%) for $C_{22}H_{18}N_2I_2$: C 46.97, H 3.20, N 4.98; found (%): C 46.92, H 3.22, N 5.01.

7,8-Dichloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry F): Reddish crystalline solid, m.p. 92-94ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 1636, 1594; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 6H), 2.26 (s, 2H), 2.34 (s, 1H), 6.78(s, 1H), 7.18 (s, 1H); MS (EI): m/z = 257 (M^+); Anal. Calcd. (%) for $C_{12}H_{14}N_2Cl_2$: C 56.05, H 5.49, N 10.89; found (%): C 56.01, H 5.56, N 10.91.

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry G): Solid, m.p. 150-152°C, IR (KBr, ν_{max}, cm^{-1}): 3320, 1631, 1597; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H), 2.95 (d, 1H, *J* = 12.8 Hz), 3.15 (d, 1H, *J* = 12.8 Hz) 3.45 (br s, 1NH), 6.55-7.0 (m, 3H), 7.15-7.35 (m, 7H), 7.55-7.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.1, 126.8, 126.9, 127.8, 128.1, 128.5, 129.5, 137.9, 139.5, 139.9, 147.4, 167.3; MS (EI): m/z = 312 [M^+], 297, 194, 103, 77, 40. Anal. Calcd. (%) for $C_{22}H_2N_2$: C 84.58, H 6.45, N 8.97; found (%): C 84.55, H 6.49, N 9.01.

2,7,8-Trimethyl-2,4-di(4-methylphenyl)-2,3-dihydro-1H-1,5-benzodiazepine (Entry H): Pale yellow crystalline solid; m.p. 102-103ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 1636, 1594; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.26-2.36 (s, 6H), 2.45 (s, 3H), 2.58 (s, 3H), 2.91(d, 1H, *J* = 12.84 Hz), 3.03 (d, 1H, *J* = 13.60 Hz), 3.29 (br s, 1NH), 6.56 (s, 1H), 7.02-7.07 (m, 1H), 7.24-7.28 (m, 4H), 7.47-7.53 (m, 2H), 7.83-7.87 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.12, 21.10, 29.88, 43.06, 72.88, 122.34, 125.24, 127.05, 128.44, 128.76, 128.94, 129.58, 129.60, 134.584, 136.562, 137.261, 137.96, 139.68, 166.76; MS (EI): m/z = 368 (M^+); Anal. Calcd. (%) for $C_{26}H_{28}N_2$: C 84.78, H 7.66, N 7.63; found (%): C 85.01, H 7.36, N 7.54.

2,4-Di(4-chlorophenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry I): Pale yellow crystalline solid, m.p. 143-145ºC; IR (KBr, ν_{max}, cm^{-1}): 3269, 1636, 1593, 765; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (s, 3H), 2.75-2.82 (d, 1H, *J* = 13.28 Hz), 2.92-3.02 (d, 1H, *J* = 13.28 Hz), 3.25 (br s, 1NH), 6.68-6.75 (m, 1H), 6.92-7.02 (m, 1H), 7.12-7.20 (m, 5H), 7.38-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.73, 42.85, 73.37, 121.43, 121.95, 126.58, 127.01, 128.23, 128.32, 128.58, 133.01,137.55, 137.72, 139.84, 145.78, 165.94; MS (EI): m/z = 381 (M^+); Anal. Calcd. (%) for $C_{22}H_{18}N_2Cl_2$: C 69.29, H 4.72, N 7.34; found (%): C 69.30, H 4.78, N 7.31.

2-Methyl-2,4-di(4-methylphenyl)-2,3-dihydro-1H-1,5-benzodiazepine (entry J): Pale yellow crystalline solid, m.p. 98-99ºC; IR (KBr,

ν_{max}, cm^{-1}): 3318, 1630, 1598; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.98 (d, 1H, *J* = 13.38 Hz), 3.05 (d, 1H, *J* = 13.38 Hz), 3.43 (br s, 1NH), 6.76 (m, 1H), 7.01 (m, 6H), 7.23 (m, 1H), 7.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.75, 21.16, 29.85, 42.97, 73.06, 121.28, 121.38, 125.18, 126.03, 127.15, 128.50, 128.67, 128.92, 129.22, 136.45, 137.0, 138.18, 139.76, 140.32, 144.98, 166.82; MS (EI): m/z = 340 (M^+); Anal. Calcd. (%) for $C_{24}H_{24}N_2$: C 84.70, H 7.05, N 8.23; found (%): C 84.68, H 7.13, N 8.18.

2-Methyl-2,4-di(4-nitrophenyl)-2,3-dihydro-1H-1,5-benzodiazepine (Entry K): Red crystalline solid, m.p. 156-158ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 1642, 1597; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 2.96 (d, 1H, *J* = 13.38 Hz), 3.27 (d, 1H, *J* = 13.38 Hz), 3.52 (br s, 1NH), 6.98 (m, 1H), 7.00 (m, 6H), 7.22 (m, 1H), 7.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.02, 42.92, 73.37, 121.29, 122.16, 123.53, 123.38, 126.78, 127.57, 127.75, 129.58, 137.23, 138.80, 144.65, 146.95, 148.40, 154.05, 163.82; MS (EI): m/z = 402 (M^+); Anal. Calcd. (%) for $C_{22}H_{18}N_4O_4$: C 65.67, H 4.47, N 13.93; found (%): C 65.65, H 4.40, N 13.98.

***In vitro* antimicrobial activity:** The antibacterial activity of the synthesized compounds were tested against *B. subtilis*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa* using nutrient agar medium (Hi-Media Laboratories, India) and the antifungal activity on *C. albicans* and *A. niger* using sabouraud dextrose agar medium (Hi-Media Laboratories, India).

Paper disc diffusion method: The sterilized[16] (autoclaved at 120°C for 0.5 h) medium (40-50°C) was innoculated (1 mL/100 mL of medium) with the suspension (10^5 cfu mL^{-1}) of the microorganism (matched to McFarland Barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (200 µg mL^{-1} in dimethyl formamide) was placed on the solidified medium. The plates were preincubated for 1 h at room temperature and incubated at 37°C for 24 and 48 h for antibacterial and antifungal activities, respectively. Ciprofloxacin (100 µg/disc) and ketoconazole (100 µg/disc) was used as standard for antibacterial and antifungal activities, respectively. The observed zone of inhibition is presented in Table-2.

Minimum inhibitory concentration (MIC)[17]: A stock solution of the synthesized compound (100 µg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and sabouraud dextrose agar medium for antifungal activity). A specified quantity of the medium (40-50°C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain *ca.* 10^5 cfu mL^{-1} and applied to plates with serially diluted compounds in dimethyl formamide

to be tested and incubated at 37°C for 24 and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is presented in Table-2.

TABLE-2
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED NOVEL 1,5-BENZODIAZEPINES (ORIGINAL STRUCTURE)

Compounds	*In vitro* activity–zone of inhibition (MIC)					
	BS	PV	KP	PA	CA	AN
A	12(1.6)	10(3)	12(1.5)	–	15(3.6)	13(>100)
B	14(2.4)	13(1.2)	13(1.8)	–	13(4.2)	11(>100)
C	13(1.5)	13(1.2)	12(3.1)	–	14(4.0)	11(>100)
D	14(3.4)	–	13(2.3)	–	15(3.8)	12(>100)
E	15(1.2)	14(1.2)	13(1.3)	11(1.2)	16(3.2)	14(>100)
F	13(1.7)	12(3.2)	11(1.7)	10(6)	14(4.6)	10(>100)
G	12(2.6)	–	12(3.2)	–	13(4.6)	11(>100)
H	14(3.0)	13(4.2)	13(1.8)	–	13(4.4)	12(>100)
I	15(3.0)	13(2.1)	12(3)	11(2.2)	12(5.2)	13(>100)
J	13(2.3)	13(1.4)	11(10.1)	10(11)	13(4.2)	11(>100)
K	14(1.4)	12(3.4)	12(3.7)	10(6)	14(4.4)	13(>100)
Ciprofloxacin 100 µg/disc	16(0.1)	15(0.12)	15(0.2)	13(0.39)	–	–
Ketoconazole 100 µg/disc	–	–	–	–	18(1.2)	17(7.2)

BS = *B. subtilis* (MTCC 1133), PV = *P. vulgaris* (MTCC 1771), KP = *K. pneumoniae* (MTCC 2405), PA = *P. aeruginosa* (MTCC 1036), CA = *C. albicans* (ATCC 2091) AN = *A. niger* (ATCC 9029).

RESULTS AND DISCUSSION

All the compounds exhibited potent antibacterial activity but less antifungal property. The compounds were active against all the tested microorganisms when compared with ciprofoxacin (standard) with a range of MIC values of 1.2-3.4, 1.2-4.2, 1.3-10.1, 1.2-11 and 3.2-5.2 µg mL^{-1} against *B. subtilis*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa* and *Candida albicans*, respectively. The compounds exhibited no activity against *A. niger*. Compound E showed potent *in vitro* antimicrobial activity with MIC of 1.2, 1.2, 1.3, 1.2, 3.2 µg mL^{-1} against *B. subtilis*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa*, *Candida albicans*. The exhibited activities of the compounds were recorded in Table-2.

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