Synthesis and Biological Evaluation of Novel Methylene-bis-[1,5]-benzodiazepines

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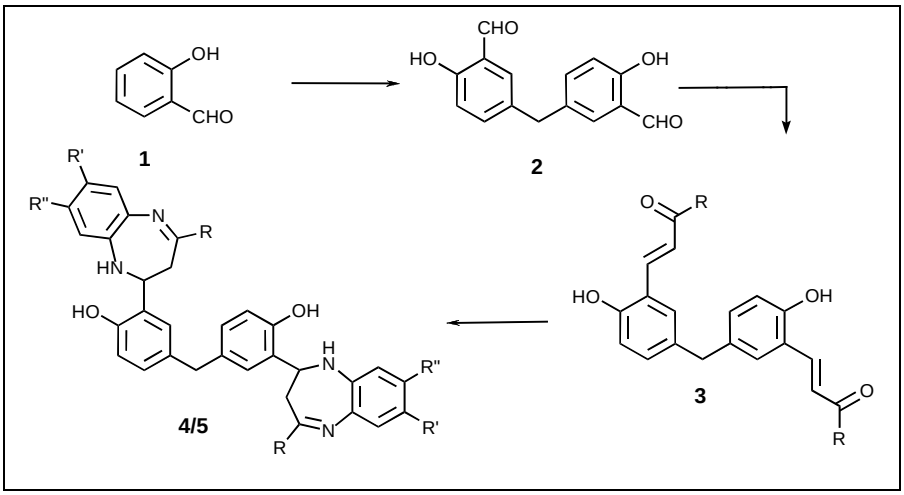

A series of novel methylene-bis-chalcones **3** was prepared by the reaction of 5-(3-formyl-4-hydroxybenzyl)-2-hydroxy benzaldehyde **2** with different acetophenones, subsequent treatment of compound **3** with an appropriate *o*-phenylenediamine gave the corresponding methylene-bis-[1,5]-benzodiazepines **4**/**5** in good yields. Characterization of the new compounds has been done by means of IR, ^{1}H NMR, MS and elemental analyses. The antibacterial and antifungal activity of the compounds has also been evaluated.

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INTRODUCTION

1,5-Benzodiazepines have received special attraction because of their pharmacological properties [1]. Many members of this family are found to be active against a variety of target types including peptide hormones (CCK) [2], inter leukin converting enzymes (ICE) [3] and potassium blockers (I_k) [4]. Nowadays the area of biological interest of 1,5-benzodiazepines has been extended to various diseases such as cancer [5], viral infection (non nucleoside inhibitors of HIV-1 reverse transcriptase) [6] and cardiovascular disorders [7]. In addition, these compounds are also used as tranquilizing, anticonvulsant, antidepressive, antibacterial, antifungal, antifeedent, anti-inflammatory and analgesic agents [8]. 1,5-Benzodiazepine derivatives are also used as dyes for acrylic fiber in photography [9]. Moreover, these are valuable synthons used for the preparation of other fused ring systems such as trioxalo [10], oxadiazolo [11], oxazino [12], triazolo [13] or furano-benzodiazepines [14].

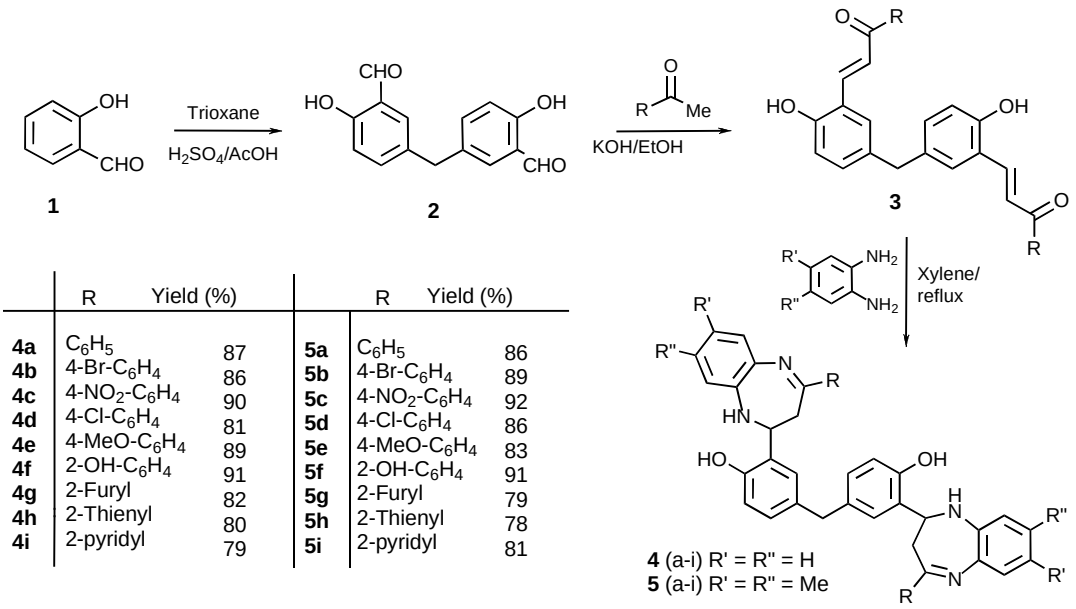
Despite their wide range of pharmacological, industrial and synthetic applications, synthesis of 1,5-benzodiazepines has received little attention except a few monomeric 1,5-benzodiazepines. These include condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds [15], β-haloketones [16] or ketones in presence of BF_3-OEt_2 [17], $NaBH_4$ [18], PPA or SiO_2 [19], $Sc(OTf)_3$ [20], $MgO/POCl_3$ [21], $Yb(OTf)_3$ [22], Al_2O_3/P_2O_5 [23], AcOH/MWI [24], Ionic liquid [25], CAN [26] and $InCl_3$ [27]. On the other hand, there are no reports on the synthesis of bis-[1,5]-benzodiazepines from any compound including α,β-unsaturated carbonyl compounds and *o*-phenylenediamines.

Inspired with the biological profile of 1,5-benzodiazepines and increasing importance in pharmaceutical and biological fields, and in continuation of our work on biologically active heterocycles [28], it was considered worthwhile to synthesize certain new chemical entities incorporating two active 1,5-benzodiazepine moieties in a single molecular framework in order to prepare molecules having with potentially enhanced biological activities and to have them evaluated for their antimicrobial activity.

RESULTS AND DISCUSSION

In this article, we describe the synthesis of 1,5-benzodiazepines from methylene-bis-chalcones 3 and *o*-phenylenediamines. For the synthesis of target compounds the 5-(3-formyl-4-hydroxybenzyl)-2-hydroxy benzaldehyde **2** was prepared by the reaction of salicylaldehyde **1** with

Scheme 1



	R	Yield (%)		R	Yield (%)
4a	C_6H_5	87	**5a**	C_6H_5	86
4b	4-Br-C_6H_4	86	**5b**	4-Br-C_6H_4	89
4c	4-NO_2-C_6H_4	90	**5c**	4-NO_2-C_6H_4	92
4d	4-Cl-C_6H_4	81	**5d**	4-Cl-C_6H_4	86
4e	4-MeO-C_6H_4	89	**5e**	4-MeO-C_6H_4	83
4f	2-OH-C_6H_4	91	**5f**	2-OH-C_6H_4	91
4g	2-Furyl	82	**5g**	2-Furyl	79
4h	2-Thienyl	80	**5h**	2-Thienyl	78
4i	2-pyridyl	79	**5i**	2-pyridyl	81

trioxane in presence of a mixture of acetic acid and conc. sulfuric acid [29], followed by condensation of compound **2** with methyl ketones in the presence of 60% aqueous KOH at room temperature [30] yields methylene-bis-chalcones **3**. The reaction times as well as the yields vary depending on the corresponding reagents. The crude product, contaminated by some starting materials, was purified by extracting with ether. The methylene-bis-chalcones **3** were reacted with an appropriate *o*-phenyl-enediamine in xylene at reflux temperature for 8 h to get methylene-bis-[1,5]-benzodiazepines **4/5** in good to excellent yields (Scheme 1). The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, MS and elemental analyses. Further, the compounds were subjected to antibacterial and antifungal testing and compared with the monomeric compounds prepared from the literature method [26,27].

Antibacterial Activity. The compounds **4a-i** and **5a-i** were screened for their antibacterial activity against human pathogenic organisms *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus typhi*. The zone of inhibition in mm at concentration 500 μg was determined using the cup plate method [31]. DMF was used as solvent control. Norfloxacin was used as antibacterial standard and the results are given in table 1. It has been observed that the compounds exhibited interesting biological activity however, with a degree of variation.

Compounds in the series **4** and **5**, which contain 4-NO_2, 4-Cl, thiophene or pyridine ring system displayed good antibacterial activity against all the organisms. Compounds **4h** and **5h** were highly active against *B. subtilis* and *S. typhi*, compounds **5c** and **5g** were highly active against *E. coli* and *B.subtilis*. Compounds **4d**, **4g**, **4i** and **5d** were highly active against *B.subtilis* and the compound **5i** was highly active against *E. coli* (Table 1). The remaining compounds showed moderate to good activity against all the organisms employed. It is interesting to note that almost all the dimeric compounds showed improved antibacterial activity than that of the corresponding monomeric compounds.

Antifungal Activity. The compounds **4a-i** and **5a-i** were also screened for their antifungal activity against *A. niger*, *C. albicans* and *E. vitae* at a concentration of 500 μg using the cup plate method [31]. The compounds **4f** and **5c** were highly active and the other compounds showed moderate to good activity. The antifungal activity of the compounds was compared with the standard drug griseofulvin. The zones of inhibition formed were measured in mm and are shown in table 1. The results reveal that almost all the dimeric compounds showed enhanced activity compared with that of their monomeric compounds.

In conclusion, we have evaluated a versatile method for the synthesis of a series of novel methylene-bis[1,5]-benzodiazepines in good to excellent yields. Some of the synthesized compounds exhibited excellent antibacterial and antifungal activity and they can be evaluated as antimicrobial agents.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merck,

Table 1

Antimicrobial activity of the compounds **4a-i** and **5a-i**.

Compound	Antibacterial activity (zone of inhibition in mm)			Antifungal activity (zone of inhibition in mm)		
	B. subtilis	*E. coli*	*S. typhi*	*A. niger*	*C albicans*	*E. vitae*
4a	15[a] (12)[b]	20[a] (12)[b]	18[a] (12)[b]	18[a] (14)[b]	18[a] (12)[b]	20[a] (12)[b]
4b	20 (14)	18 (13)	18 (14)	20 (12)	19 (14)	19 (12)
4c	22 (17)	22 (16)	20 (16)	23 (13)	21 (13)	18 (14)
4d	23 (17)	21 (15)	21 (15)	25 (16)	22 (15)	24 (15)
4e	21 (16)	15 (11)	16 (11)	18 (14)	18 (14)	22 (13)
4f	22 (19)	21 (12)	19 (13)	24 (15)	25 (17)	25 (17)
4g	24 (22)	22 (16)	20 (15)	26 (17)	22 (14)	23 (15)
4h	25 (20)	22 (16)	23 (17)	26 (19)	21 (12)	24 (17)
4i	23 (19)	22 (13)	21 (17)	24 (16)	18 (11)	20 (15)
5a	18 (14)	21 (19)	17 (11)	18 (12)	19 (11)	18 (12)
5b	21 (16)	19 (17)	17 (11)	18 (13)	18 (12)	19 (14)
5c	23 (21)	24 (18)	19 (13)	25 (16)	27 (19)	23 (13)
5d	23 (20)	21 (16)	18 (14)	24 (14)	20 (14)	23 (16)
5e	19 (11)	21 (15)	15 (10)	18 (13)	18 (13)	19 (14)
5f	20 (10)	21 (17)	16 (10)	24 (17)	24 (17)	22 (15)
5g	25 (19)	23 (18)	19 (16)	19 (14)	24 (15)	18 (12)
5h	26 (20)	22 (16)	24 (16)	24 (15)	25 (14)	20 (12)
5i	21 (19)	24 (18)	20 (15)	26 (17)	21 (13)	23 (15)
Norfloxacin	26	28	26	-	-	-
Griseofulvin	-	-	-	30	30	30

Note: <16mm, inactive; 17-23mm, moderately active; 23-26mm, highly active. [a]Activity of dimeric compounds; [b]Activity of their monomeric compounds.

$60_{F\text{-}254}$). IR spectra were obtained on a Perkin-Elmer FTIR 5000 spectrophotometer, using KBr pellets. ^{1}H NMR spectra were obtained with a Varian Gemini 300 MHz spectrometer and the chemical shifts were reported as parts per million (δ ppm) down field using TMS as an internal standard. Mass spectra were obtained on a VG micro mass 7070H spectrometer operating at 70 eV. UV spectra were obtained on a UV-2401 spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. All solvents and chemicals were purchased from Sigma Aldrich chemical company and used without further purification.

Synthesis of (*E*)-3-(4-bromophenyl)-1-(5,3-[(*E*)-3-(4-bromophenyl)-2-propenoyl]-4-hydroxy-benzyl-2-hydroxyphenyl)-2-propen-1-one (3). A solution of 2 (2.56 g, 0.01 mol) and 4-bromoacetophenone (0.02 mol) in 20 mL ethanol was slowly treated with 20 mL 60% KOH solution at 5-10 °C. The reaction was stirred at room temperature until TLC indicated complete conversion (4 h). It was then diluted with 50 mL water and extracted with 3x20 mL diethyl ether. The aqueous solution was acidified with dilute HCl. The solid obtained was filtered, washed thoroughly with water and dried. Crystallization of the crude residue from toluene: MeOH (3:2) afforded 91% of 3 as a yellow solid; mp 160-162 °C. UV (EtOH, nm) λ_{max}: 370.5, 304.9, 268.1; IR (KBr): 3440, 3056, 1640, 1571, 1482, 1224 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.84 (2H, s, -CH_2), 6.84 (2H, d, J = 15.2 Hz, β-*H*), 7.70 (2H, d, J = 15.2 Hz, α-*H*), 10.21 (2H, s, O*H*), 7.18 (4H, d, J = 9.1 Hz, Ar*H*), 8.05 (4H, d, J = 9.1 Hz, Ar*H*), 7.82-8.18 (6H, m, Ar*H*); MS: m/z 616 (M$^+$). *Anal.* calcd. for $C_{31}H_{22}O_4Br_2$: C, 60.19; H, 3.67; Br, 25.78. Found: C, 60.12; H, 3.59; Br, 25.61. The other chalcones **3** were prepared by the similar procedure and confirmed their structures from the IR, ^{1}H NMR, MS and elemental analyses [30].

General procedure for the synthesis of methylene-bis-[1,5]-benzodiazepines (4/5). To a solution of **3** (0.01 mol) in 40 mL xylene, boiling solution of an appropriate *o*-phenylene-diamine (0.02 mol) in 20 mL xylene was added in small portions and the reaction mixture was refluxed for 8 h (TLC). During the reaction, formed water was separated by using Dean-Stark apparatus. The reaction mixture left for 24 h at room temperature, and excess solvent was distilled off under reduced pressure. The residual mass was triturated with light petroleum ether; solid obtained was filtered and recrystallized from ethanol to give pure 4/5.

4-[4-Hydroxy-3-(4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)benzyl]-2-(4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)phenol (4a). This compound was obtained as yellow solid; mp 80-82 °C; IR (KBr): ν 3354, 3056, 1507, 1282, 1101, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.18 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.37-7.32 (14H, m, Ar*H*), 7.42-7.91 (10H, m, Ar*H*). MS: m/z 640 (M$^+$). *Anal.* calcd. for $C_{43}H_{36}N_4O_2$: C, 80.60; H, 5.66; N, 8.74. Found: C, 80.75; H, 5.57; N, 8.69.

2-[4-(4-Bromophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(4-bromophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (4b). This compound was obtained as brown solid; mp 78-80 °C; IR (KBr): 3352, 3042, 1500, 1281, 1110, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ: 3.21 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.39 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.0 (2H, bs, N*H*), 5.21 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.37-7.30 (14H, m, Ar*H*), 7.41 (4H, d, J = 8.4 Hz, Ar*H*),7.98 (4H, d, J = 8.4 Hz, Ar*H*); MS: m/z 798 (M$^+$). *Anal.* calcd. for $C_{43}H_{34}Br_2N_4O_2$: C, 64.67; H, 4.29; N, 7.02. Found: C, 64.21; H, 4.17; N, 7.00.

4-4-Hydroxy-3-[4-(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (4c). This compound was obtained as brown solid; mp 166-168 °C; IR (KBr): 3352, 3042, 1502, 1482, 1347, 1281, 1110, 743 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.0 (2H, bs, N*H*), 5.19 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.37-7.32 (14H, m, Ar*H*), 8.1 (4H, d, J = 8.9 Hz, Ar*H*), 8.32 (4H, d, J = 8.9 Hz, Ar*H*); MS: m/z 730 (M^+). *Anal.* calcd. for $C_{43}H_{34}N_6O_6$: C, 70.67; H, 4.69; N, 11.50. Found: C, 70.10; H, 4.52; N, 11.32.

2-[4-(4-Chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(4-chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (4d). This compound was obtained as pale brown solid; mp 99-101 °C; IR (KBr): 3351, 3051, 1502, 1280, 1100, 742, 686 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.40 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 4.0 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.36-7.30 (14H, m, Ar*H*), 7.39 (4H, d, J = 8.2 Hz, Ar*H*), 7.91 (4H, d, J = 8.2 Hz, Ar*H*); MS: m/z 710 (M^+). *Anal.* calcd. for $C_{43}H_{34}Cl_2N_4O_2$: C, 72.78; H, 4.83; N, 7.89. Found: C, 71.90; H, 4.77; N, 7.61.

4-4-Hydroxy-3-[4-(4-methoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(4-methoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (4e). This compound was obtained as yellow solid; mp 77-79 °C; IR (KBr): 3354, 3049, 1502, 1271, 1290, 1100, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.6 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 3.90 (6H, s, CH_3), 4.0 (2H, bs, N*H*), 5.20 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.36-7.30 (22H, m, Ar*H*); MS: m/z 700 (M^+). *Anal.* calcd. for $C_{45}H_{40}N_4O_4$: C, 77.12; H, 5.75; N, 7.99. Found: C, 78.00; H, 5.67; N, 7.83.

4-4-Hydroxy-3-[4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (4f). This compound was obtained as orange solid; mp 110-112 °C; IR (KBr): 3454-3357, 3032, 1502, 1280, 1102, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.08 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.52 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 5.24 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.42 (2H, bs, N*H*), 6.52-7.30 (22H, m, Ar*H*); MS: m/z 672 (M^+). *Anal.* calcd. for $C_{43}H_{36}N_4O_4$: C, 76.77; H, 5.39; N, 8.33. Found: C, 75.61; H, 5.23; N, 8.27.

2-[4-(2-Furyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(2-furyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzyl phenol (4g). This compound was obtained as brown solid; mp 141-143 °C; IR (KBr): 3352, 3037, 1503, 1595, 1282, 1107, 1030, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.19-7.32 (18H, m, Ar*H*), 7.61 (2H, d, J = 6.8 Hz, Ar*H*); MS: m/z 620 (M^+). *Anal.* calc. for $C_{39}H_{32}N_4O_4$: C, 75.47; H, 5.20; N, 9.03. Found: C, 76.01; H, 5.05; N, 8.89.

4-4-Hydroxy-3-[4-(2-thienyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(2-thienyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (4h). This compound was obtained as brown solid; mp 115-117 °C; IR (KBr): 3352, 3037, 1503, 1596, 1282, 1105, 1037, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.12 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.46 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.49-7.30 (18H, m, Ar*H*), 7.40 (2H, s, Ar*H*); MS: m/z 652 (M^+). *Anal.* calcd. for $C_{39}H_{32}N_4O_4$: C, 71.75; H, 4.94; N, 8.58. Found: C, 71.26; H, 4.83; N, 8.22.

4-4-Hydroxy-3-[4-(2-pyridyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(2-pyridyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (4i). This compound was obtained as yellow-brown solid; mp 162-164 °C; IR (KBr): 3352, 3035, 1630, 1592, 1503, 1470, 1282, 1105, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (2H, dd, J_{ab} = 13.5, J_{ax} = 8.6 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.5, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.6, J_{xb} = 3.2 Hz, H_x), 6.47-7.32 (16H, m, Ar*H*), 7.50-7.60 (2H, m, Ar*H*), 8.61 (2H, d, J = 8.32 Hz, Ar*H*); MS: m/z 642 (M^+). *Anal.* calcd. for $C_{41}H_{34}N_6O_2$: C, 76.62; H, 5.33; N, 13.07. Found: C, 76.31; H, 5.26; N, 12.87.

2-(7,8-Dimethyl-4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4-[3-(7,8-dimethyl-4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4-hydroxybenzyl]phenol (5a). This compound was obtained as brown solid; mp 92-94 °C; IR (KBr): 3352, 3049, 1502, 1281, 1110, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, CH_3), 3.12 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.42 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.20 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.78 (2H, d, J = 9.1 Hz, Ar*H*), 6.96 (2H, s, Ar*H*), 7.0 (2H, d, J = 9.1 Hz, Ar*H*), 7.29-7.90 (12H, m, Ar*H*); MS: m/z 696 (M^+). *Anal.* calcd. for $C_{47}H_{44}N_4O_2$: C, 81.01; H, 6.36; N, 8.04. Found: C, 81.31; H, 6.21; N, 7.93.

2-[4-(4-Bromophenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(4-bromophenyl)-7,8-dimeth-yl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (5b). This compound was obtained as yellow-brown solid; mp 101-103 °C; IR (KBr): 3350, 3041, 1507, 1281, 1107, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.12 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.42 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.04 (2H, bs, N*H*), 5.20 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.78 (2H, d, J = 9.1 Hz, Ar*H*), 6.96 (2H, s, Ar*H*), 7.0 (2H, d, J = 9.1 Hz, Ar*H*), 7.29-7.39 (6H, m, Ar*H*), 7.87 (4H, d, J = 8.2 Hz, Ar*H*); MS: m/z 854 (M^+). *Anal.* calcd. for $C_{47}H_{42}Br_2N_4O_2$: C, 66.05; H, 4.95; N, 6.56. Found: C, 65.81; H, 4.86; N, 6.53.

2-[7,8-Dimethyl-4-(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[7,8-dimethyl-4-(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (5c). This compound was obtained as orange solid; mp 173-175 °C; IR (KBr): 3350, 3042, 1502, 1487, 1344, 1281, 1110, 743 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.12 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.42 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.21 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.77 (2H, d, J = 9.1 Hz, Ar*H*), 6.96-7.10 (4H, m, Ar*H*), 7.27 (2H, s, Ar*H*), 8.01 (4H, d, J = 8.4 Hz, Ar*H*), 8.27 (4H, d, J = 8.4 Hz, Ar*H*); MS: m/z 786(M^+). *Anal.* calcd. for $C_{47}H_{42}N_6O_6$:C, 71.74; H, 5.38; N, 10.68. Found:C,71.50; H, 5.26; N, 10.51.

2-[4-(4-Chlorophenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(4-chlorophenyl)-7,8-dimeth-yl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzyl-phenol (5d). This compound was obtained as pale brown solid; mp 121-123 °C; IR (KBr): 3351, 3036, 1502, 1284, 1107, 742, 686 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.12 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.42 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.72 (2H, d, J = 9.1 Hz, Ar*H*), 6.92-7.10 (4H, m, Ar*H*), 7.28-7.32 (6H, m, Ar*H*), 7.77 (4H, d, J = 8.3 Hz, Ar*H*); MS: m/z 766 (M^+). *Anal.* calcd.

for $C_{47}H_{42}Cl_2N_4O_2$: C, 73.72; H, 5.53; N,7.32. Found: C, 73.67; H, 5.41; N, 7.30.

4-4-Hydroxy-3-[4-(4-methoxyphenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(4-methoxyphenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (5e). This compound was obtained as yellow solid; mp 94-96 °C; IR (KBr): 3352, 3036, 1502, 1287, 1271, 1107, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.12 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.42 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 3.91 (6H, s, -CH_3), 4.04 (2H, bs, N*H*), 5.20 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.78 (2H, d, J = 9.1 Hz, Ar*H*), 6.85 (4H, d, J = 8.4 Hz, Ar*H*), 6.96 (2H, s, Ar*H*), 7.05 (6H, m, Ar*H*), 7.32 (2H, s, Ar*H*); MS: m/z 756 (M^+). *Anal.* calcd. for $C_{49}H_{48}N_4O_4$: C, 77.75; H, 6.39; N, 7.40. Found: C, 78.01; H, 6.21; N, 7.32.

4-4-Hydroxy-3-[4-(2-hydroxyphenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]benzyl-2-[4-(2-hydroxyphenyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]phenol (5f). This compound was obtained as orange solid; mp 134-136 °C; IR (KBr): 3452-3357, 3033, 1507, 1284, 1107, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, CH_3), 3.45 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.66 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.80 (2H, s, -CH_2), 6.51 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.76 (2H, d, J = 9.1 Hz, Ar*H*), 6.97-7.32 (14H, m, Ar*H*); MS: m/z 728 (M^+). *Anal.* calcd. for $C_{47}H_{44}N_4O_4$: C, 77.45; H, 6.09; N, 7.69. Found: C, 77.01; H, 6.01; N, 7.51.

2-[4-(2-Furyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[4-(2-furyl)-7,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (5g). This compound was obtained as black solid; mp 151-153 °C; IR (KBr): 3352, 3037, 1595, 1503, 1282, 1107, 1030, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.32 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.49 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.01 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.19-6.27 (4H, m, Ar*H*), 6.76 (2H, d, J = 9.1 Hz, Ar*H*), 6.87-7.0 (6H, m, Ar*H*), 7.27 (2H, s, Ar*H*), 7.61 (2H, d, J = 8.3 Hz, Ar*H*); MS: m/z 676 (M^+). *Anal.* calcd. for $C_{43}H_{40}N_4O_4$: C, 76.31; H, 5.96; N, 8.28. Found: C, 76.06; H, 5.81; N, 8.22.

2-[7,8-Dimethyl-4-(2-thienyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[7,8-dimethyl-4-(2-thienyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (5h). This compound was obtained as brown solid; mp 119-121 °C; IR (KBr): 3352, 3037, 2971, 1596, 1503, 1281, 1110, 1037, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, -CH_3), 3.21 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.41 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.84 (2H, s, -CH_2), 4.05 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.76-7.10 (12H, m, Ar*H*), 7.32 (2H, s, Ar*H*); MS: m/z 708 (M^+). *Anal.* calcd. for $C_{43}H_{40}N_4O_2S_2$: C, 72.85; H, 5.69; N, 7.90. Found: C, 73.06; H, 5.57; N, 7.79.

2-[7,8-Dimethyl-4-(2-pyridyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-3-[7,8-dimethyl-4-(2-pyridyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl]-4-hydroxybenzylphenol (5i). This compound was obtained as brown solid; mp 147-149 °C; IR (KBr): 3352, 3035, 1630, 1592, 1503, 1470, 1282, 1105, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (12H, s, CH_3), 3.14 (2H, dd, J_{ab} = 13.6, J_{ax} = 8.7 Hz, H_a), 3.39 (2H, dd, J_{ba} = 13.6, J_{bx} = 3.2 Hz, H_b), 3.82 (2H, s, -CH_2), 4.04 (2H, bs, N*H*), 5.22 (2H, dd, J_{xa} = 8.7, J_{xb} = 3.2 Hz, H_x), 6.27 (2H, s, Ar*H*), 6.80-7.0 (8H, m, Ar*H*), 7.32 (2H, d, J = 8.3 Hz, Ar*H*), 7.52-7.59 (4H, m, Ar*H*), 8.62 (2H, d, J = 8.7 Hz, Ar*H*); MS: m/z 698 (M^+). *Anal.* calcd. for $C_{45}H_{42}N_6O_2$: C, 77.34; H, 6.06; N, 12.03. Found: C, 77.02; H, 6.00; N, 11.89.

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REFERENCES AND NOTES

[1a] Steernbach, L. H. *Angew. Chem.* Int. Ed. Engl. **1971**, *10*, 34. b) Schutz, H. Benzodiazepine, Springer, Heidelberg, **1982**, *2*, 240. c) Smalley, R. K.; Barton, D.; Olli's, W. D. (Eds), *In Comprehensive Organic Chemistry,* Pergamon, Oxford, **1979**, *4*, 600.

[2] Werner, W.; Baumgart, J.; Burckhardt, G.; Fleck, W. F.; Geller, K.; Gutsche, W.; Hanschmann, H.; Messerschmidt, A.; Roemer, W. *Biophys. Chem.* **1990**, *35*, 271.

[3] Herpin, T. F.; Van Kirk, K. G.; Salvino, J. M.; Yu, S. T.; Labaudiniere, R. F. *J. Comb. Chem.* **2000**, *5*, 513.

[4] Claremon, D. A.; Liverton, N.; Selnick, H. G.; Smith, G. R. PCT Int. Appl. **1996**, WO9640653.

[5] Atwal, K. S.; Bergey, J. L.; Hedberg, A.; Moreland, S. *J. Med. Chem.* **1987**, *30*, 635.

[6] Merluzzi, V.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C. -K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. *Science*. **1990**, *250*, 1411.

[7a] Di Braccio, M.; Grossi, G.; G. Roma, G.; Vargiu, L.; Mura, M.; Marongiu, M. E. *Eur. J. Med. Chem* **2001**, *36*, 935. b) Tranquillini, M. E.; Cassara, P. G.; Corsi, M.; Curotto, G.; Donati, D.; Finizia, G.; Pentassuglia, G.; Polinelli, S.; Tarzia, G.; Ursini, A.; Van Amsterdam, F. T. M. *Arch. Pharm.***1997**, *330*, 353.

[8] Landquist, J. K.; *In Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W. Eds. Pergamon: Oxford, **1984**, *1*, 166-170.

[9a] Haris, R. C.; Straley, J. M. US Patent **1968**, 1537757. b) *Chem. Abstr.* **1970**, *73*, 100054w.

[10] Aversa, M. C.; Ferlazzo, A.; Giannetto, P.; Kohnke, F. H. *Synthesis*. **1986**, 230.

[11] Chimirri, A.; Grasso, S.; Ottana, R.; Romeo, G.; Zappala, M. *J. Heterocyclic Chem.* **1990**, *27*, 371.

[12] Sl-Sayed, A. M.; Abdel-Ghany, H.; El-Saghier, A. M. M. *Synth. Commun.* **1999**, *29*, 3561.

[13a] Essaber, M.; Baouid, A.; Hasnaoui, A.; Benharref, A.; Lavergne, J. P. *Synth. Commun.* **1998**, *28*, 4097. b) Xu, J. X.; Wu, H. T.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 84. c) Zhang, X. Y.; Xu, J. X.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 404.

[14] Reddy, K. V. V.; Rao, P. S.; Ashok, D. *Synth. Commun.* **2000**, *30*, 1825.

[15] Stahlofen, P.; Ried, W. *Chem. Ber.* **1957**, *90*, 815.

[16] Ried, W.; Torinus, E. *Chem. Ber.* **1959**, *92*, 2902.

[17] Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans 1* **1974**, 2657.

[18] Morales, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles*. **1986**, *24*, 135.

[19] Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun.* **1999**, *29*, 1941.

[20] De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1811.

[21] Balakrishna, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, *42*, 1127.

[22] Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193.

[23] Kaboudin, B.; Navaee, K. *Heterocycles*. **2001**, *55*, 1443.

[24a] Minothora, P.; Julia, S. S.; Constantinos, A. *Tetrahedron Lett.* **2002**, *43*, 1755. b) Kaboudin, B.; Navaee, K. *Heterocycles.* **2001**, *55*, 1443.

[25] Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1835.

[26] Ravi, V.; Ramu, E.; Sreelatha, N.; Srinivas, R. A. *Synlett*. **2006**, 1009

[27] Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Stinivasulu, G.; Kunwar, A. C. *Arkivoc* **2005**, *3*, 221.

[28] Smitha, G.; Sanjeeva Reddy, Ch. *Synth. Commun*. **2006**, *36*, 1795.

[29] Marvel, C. S.; Turkey, N. *J. Am. Chem. Soc.,* **1957**, *79*, 6000.

[30] Sanjeeva Reddy, Ch.; Nagaraj, A. *J. Heterocyclic Chem.* **2007**, *44*, 1181.

[31] Seely, H. W.; Van Denmark, P. J. Microbes in action: *A laboratory manual of microbiology*, (D. B. Taraporevala Sons & Co. Pvt. Ltd, Bombay), **1975**, 55. b) Barry, A. I. *The antimicrobial Susceptibility Test*, Principles and Practices, 4th Ed (ELBS), **1976**, 80.