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Synthesis and biological study of novel methylene-bis-benzofuranyl-[1,5]-benzothiazepines

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Abstract: A series of novel methylene-bis-[1,5]-benzothiazepines **4** and methylene-bis-benzofuranyl-[1,5]-benzothiazepines **5** were prepared by the reaction of methylene-bis-chalcones **3** with 2-aminothiophenol followed by the condensation with *α*-bromoacetophenone. The structures of the synthesized compounds were confirmed by their IR, ^{1}H, ^{13}C NMR and Mass spectral analyses. All the synthesized compounds were tested for their antimicrobial activity against Gram-positive, Gram-negative bacteria and fungi. Among the synthesized compounds, the compounds **4f**, **4g**, **5f** and **5g** were found to be the most active against *Bacillus subtilis*, *Bacillus sphaericus*, *Staphylococcus aureus*, *Klebsiella aerogenes* and *Chromobacterium violaceum*. Similarly these compounds showed potent antifungal effect against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. It is interesting to note that the compounds with heterocyclic ring substituents at the 4th position of benzothiazepine system displayed notable antibacterial activity, almost equal to that of streptomycin and penicillin.

Keywords: Methylene-bis-[1,5]-benzothiazepines, Methylene-bis-benzofuranyl-[1,5]-benzothiazepines, Antibacterial activity, Antifungal activity.

1. Introduction

Benzothiazepine and its derivatives show a wide spectrum of pharmacological activities such as antifeedent[1], coronary vasodilatory[2], tranquilizer[3], antidepressant[4], CNS stimulant[5], antihypertensive[6], calcium channel blocker[7], antiulcer[8], calcium antagonist[9] and antimicrobial agents.[10,11] Benzothiazepine derivatives have been reported to be more potent selective inhibitors of the mitochondrial Na^{+}–Ca^{2+} exchangers.[12]

Several naturally occurring and synthetic benzofuran derivatives are known to be associated with biological and pharmacological activities such as anti-inflammatory[13], anti-implantation[14], anticancer[15-17], pesticidal[18], nematicidal[19], antiuterotropic[20] activities. The applications of benzofuran derivatives were also extended to textile and paper industries.[21] Owing to their well known bioactivities, the synthesis and chemical transformations of various groups of benzothiazepines have been studied and the procedures used have also been summarized.[22-26] Most of the synthetic methods used for their preparation are based on the reaction of *α*,*β*-unsaturated ketones or exocyclic *α*,*β*-

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unsaturated ketones with 2-aminothiophenol which provided the related tetracyclic benzothiazepines.[27-28] Similarly, benzofuran synthesis based on MacLeod's procedure is well documented.[29-31]

Inspired with the biological profile of 1,5-benzothiazepine and benzofuran derivatives, in continuation of our work on biologically active heterocycles[32-45], and in order to know the combined effect of both 1,5-benzothiazepine and benzofuran on biological activity, it was considered worth-while to synthesize certain new chemical entities incorporating two active pharmacophores such as benzothiazepine and benzofuran in a single molecular frame work and to get them evaluated for their antimicrobial activity. However, the synthesis of dimeric compounds with 1,5-benzothiazepine and benzofuran moieties has been hitherto unreported.

The synthetic pathway followed by MacLeod *et al*., has been employed to prepare the title compounds, where the cyclodehydration of alkoxyketones to benzofuran has been carried out in alkaline medium instead of the generally used acids.

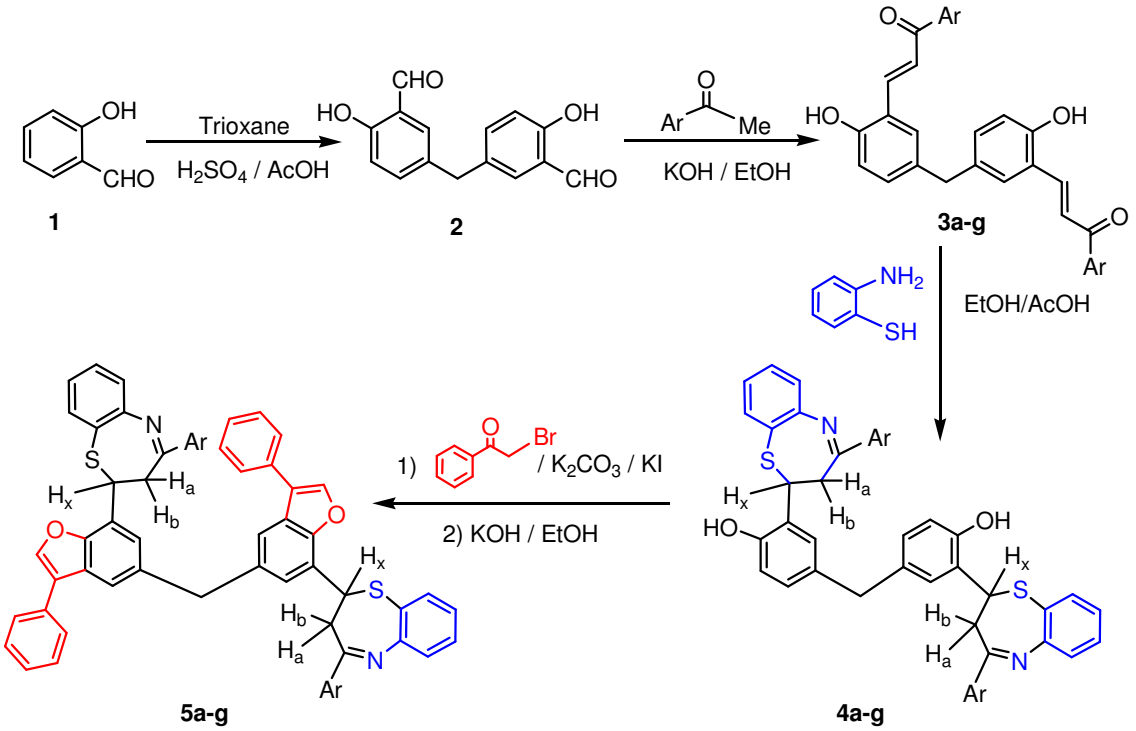
2. Results and Discussion

We describe herein the synthesis of methylene-bis-[1,5]-benzothiazepines **4** and methylene-bis-benzofurano-[1,5]-benzothiazepines **5** from methylene-bis-chalcones **3**. For the synthesis of target compounds, first, the 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde **2** was prepared by the reaction of salicylaldehyde **1** with trioxane in presence of a mixture of acetic acid and conc. sulfuric acid.[46] The condensation of compound **2** with methyl ketones in the presence of 60% aqueous KOH at room temperature afforded methylene-bis-chalcones **3**. The reaction durations 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 **3a-g** were reacted with 2-aminothiophenol, in ethanol in the presence of acetic acid at reflux temperature for 4 h, to get methylene-bis-[1,5]-benzothiazepines **4a-g** in good to excellent yields. The structure of the synthesized compounds was confirmed by IR, ^{1}H, ^{13}C NMR and Mass spectra. Further, the compounds **4a-g** on condensation with α-bromoacetophenone, in the presence of anhydrous K_2CO_3/dry acetone and catalytic amount of KI, followed by cyclization in ethanolic KOH gave methylene-bis-benzofurano-[1,5]-benzothiazepines **5a-g** (**Scheme 1**), which were purified by column chromatography using silica gel (60-120 mesh) and petrol ether (60-80 °C). The mechanism as established by MacLeod *et al*. is an intramolecular Aldol condensation in which the phenoxide ion formed promotes the attack at the exocyclic carbonyl function through the resonance stabilized carbanion generated at the *para* position, relative to the phenoxide ion. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction, on acidification, water is spontaneously eliminated from the labile β-hydroxydihydrofuran ring system to give the unsaturated benzofuran system. The products **5a-g** were characterized by IR, ^{1}H, ^{13}C NMR and Mass spectra.

2.1. Antibacterial Activity

The *in vitro* antibacterial activities of the methylene-bis-[1,5]-benzothiazepines **4a-g** and methyelne-bis-benzofurayl-[1,5]-benzothiazepines **5a-g** were assessed against three representative Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), and *Staphylococcus aureus* (MTCC 96), three Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39) and *Chromobacterium violaceum* (MTCC 2656), by the broth dilution method recommended by National Committee for Clinical Laboratory Standards.[47] Bacteria were grown overnight in Luria Bertani (LB) broth at 37°C, harvested by centrifugation, and

then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO.



Ar = a) C_6H_5; **b**) 4-Br-C_6H_4; **c**) 4-Cl-C_6H_4; **d**) 4-MeO-C_6H_4; **e**) 4-O_2N-C_6H_4; **f**) 2-furyl; **g**) 2-pyridyl

Scheme 1. Synthetic pathway for compounds **5a-g**.

Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 μg/mL. Ten microliters of the broth containing about 10^5 colony-forming units (cfu)/mL of test bacteria wasere added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C, and the growth was monitored by visually and spectrophotometrically. Penicillin and Streptomycin were also screened under identical conditions for comparison. Data of the compounds **4a-g** and **5a-g** are presented in Table 1 as the minimal inhibitory concentration (MIC, μg/mL). It has been observed that the compounds exhibited interesting biological activity however, with a degree of variation.

In the series **4a-g** and **5a-g**, the compounds **4g**, **5g** were found to be the most active against Gram-positive and Gram-negative bacteria except *P.aeruginosa*. The compound **5f** is highly active against all the three Gram-positive bacteria and *K.aerogens*, the compounds **4d**, **4f** were active against *B. subtilis* and **4d**, **4f**, and **5d** were active against *B.sphaericus*. The remaining compounds showed moderate to good activity against all the organisms employed except *P.aeruginosa*. It is interesting to note that the compounds in which thiazepine ring is substituted at 4^{th} position by the heterocyclic rings, displayed notable antibacterial activity almost equal to that of streptomycin and penicillin (Table 1). However, this trend was translated exactly to antifungal activity.

2.2. Antifungal Activity

The *in vitro* antifungal activities of the methylene-bis-[1,5]-benzothiazepines **4a-g** and methylene-bis-benzofuranyl-[1,5]-benzothiazepines **5a-g** were assessed against four fungal organisms *viz*. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996)**.** *C.albican*s was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation, and then washed twice with sterile distilled water. *A.fumigatus*, *T.rubrum*, and *T.mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of 10^5 spores/mL. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for about 48 to 72 h at 28 °C. The antifungal activity of each compound was compared with the standard drug Amphotericin B. Minimum inhibitory concentration (MIC, μg/mL) was measured and compared with controls, the MIC values of the compounds screened are given in Table 2.

The antifungal activity of the compounds in **4a-g** and **5a-g** series, the compound **5f** is highly active against all the micro organisms employed. The compounds **5e**, **5g** were highly active against all the organisms except *C.albicans*, similarly the compound **4g** is also highly active against all the organisms except *T.rubrum*. The remaining compounds showed moderate to good activity (Table 2).

3. Conclusions

In conclusion, a series of novel methylene-bis-[1,5]-benzothiazepines and methylene-bis-benzofuranyl-[1,5]benzothiazepines were prepared. The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria and fungi. Most of the compounds showed a moderate degree of antimicrobial activity. Among them, compounds **4g**, **5f** and **5g** were found to be the most active against all the microorganisms employed both for antibacterial and antifungal activity. With this set of analogues, we are now in a position to investigate the multiple biological activities of these compounds.

4. Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Purity of the compounds was checked using precoated TLC plates. IR spectra were recorded on a Perkin-Elmer FTIR 5000 spectrometer, using KBr discs. ^{1}H, ^{13}C NMR spectra in DMSO-d_6 were recorded on 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 micromass 7070H spectrometer. All the solvents and chemicals were purchased from Sigma-Aldrich chemical company and used without further purification.

4.1. Synthesis of (E)-3-(4-bromophenyl)-1-(5,3-[(E)-3-(4-bromophenyl)-2-propenoyl]-4-hydroxybenzyl-2-hydroxyphenyl)-2-propen-1-one (3b):

A solution of **2** (1 mmol) and *p*-bromoacetophenone (2 mmol) in 20 mL ethanol was slowly treated with 20 mL of 60% aqueous KOH solution at 5-10°C. The reaction mixture was stirred at room temperature until TLC indicated complete conversion (4h). 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 **3b** as yellow solid; m.p. 160-162°C, IR (KBr): ν 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 = 16.4

Hz, α-H), 7.18 (4H, d, *J* = 9.1 Hz, ArH), 7.70 (2H, d, *J* = 16.4 Hz, β-H), 8.05 (4H, d, *J* = 9.1 Hz, ArH), 8.18-7.82 (6H, m, ArH), 10.21 (2H, s, OH); MS: *m/z* (%) 616 (100, M^+), 461 (86), 433 (46), 407 (21), 371 (22). *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 compounds **3** were prepared by the similar procedure and confirmed their structures from IR, ^{1}H NMR, MS and elemental analyses.[37]

Table 1. Antibacterial Activity of Compounds **4a-g** and **5a-g**

Compound	Minimum inhibitory concentration (MIC, μg/mL)					
	Gram-positive			Gram-negative		
	B.subtilis	*B.sphaericus*	*S.aureus*	*P.aeruginosa*	*K.aerogenes*	*C.violaceum*
4a	12.5	12.5	25.0	–	50.0	25.0
4b	25.0	12.5	25.0	–	50.0	50.0
4c	12.5	25.0	12.5	–	6.25	12.5
4d	6.25	6.25	12.5	25.0	12.5	12.5
4e	25.0	50.0	25.0	–	50.0	50.0
4f	6.25	6.25	12.5	12.5	6.25	12.5
4g	6.25	6.25	12.5	–	6.25	6.25
5a	25.0	12.5	25.0	–	12.5	12.5
5b	50.0	50.0	50.0	–	–	50.0
5c	25.0	12.5	12.5	–	25.0	6.25
5d	12.5	6.25	25.0	–	25.0	12.5
5e	50.0	50.0	25.0	–	12.5	25.0
5f	6.25	6.25	6.25	25.0	6.25	12.5
5g	6.25	6.25	6.25	–	12.5	6.25
Streptomycin	6.25	12.5	6.25	1.56	1.56	3.12
Penicillin	1.56	3.12	1.56	6.25	6.25	12.5

Microorganisms: Bacillus subtilis MTCC 441; Bacillus sphaericus MTCC 11; Staphylococcus aureus MTCC 96; Pseudomonas aeruginosa MTCC 741; Klebsiella aerogenes MTCC 39; and Chromobacterium violaceum MTCC 2656.

Table 2. Antifungal Activity of Compounds **4a-g** and **5a-g**

Compound	Minimum inhibitory concentration (MIC, μg/mL)			
	C. albicans	*A.fumigatus*	*T.rubrum*	*T.mentagrophytes*
4a	50.0	50.0	50.0	25.0
4b	50.0	25.0	50.0	25.0
4c	12.5	6.25	6.25	25.0
4d	25.0	25.0	12.5	25.0
4e	50.0	100	100	100
4f	6.25	12.5	25.0	12.5
4g	6.25	6.25	12.5	6.25
5a	50.0	100	50.0	25.0
5b	50.0	25.0	25.0	25.0
5c	12.5	6.25	6.25	12.5
5d	50.0	25.0	100	100
5e	12.5	6.25	6.25	6.25
5f	6.25	6.25	6.25	6.25
5g	12.5	6.25	6.25	6.25
Amphotericin B	6.25	3.12	3.12	3.20

Microorganisms: Candida albicans ATCC 19231; Aspergillus fumigatus HIC 6094; Trichophyton rubrum IFO 9185; Trichophyton mentagrophytes IFO 40996.

4.2. General procedure of the synthesis of methylene-bis-[1,5]-benzothiazepines (4a-g):

Ethanolic solution (50 mL) of methylene-bis-chalcone **3** (1 mmol) was refluxed with 2-amino-thiophenol (2 mmol) and few drops of glacial acetic acid for 4 h. At the end of the reaction, the ethanolic solution was concentrated to half of its volume under reduced pressure. The solid that separated from the concentrate was filtered and recrystallized from benzene: petrol ether (8:2 v/v) as yellow needles. All the products were characterized by ^{1}H, ^{13}C NMR, IR and Mass spectra.

4.2.1. 4-[4-Hydroxy-3-(4-phenyl-2,3-dihydro-1,5-benzothiazepin-2-yl)-benzyl]-2-(4-phenyl-2,3-dihydro-1,5-benzothiazepin-2-yl)phenol (4a). Yellow solid; m.p. 189-191°C; IR (KBr): *v* 3438, 3061, 1687, 1575, 1449, 1406 cm^{-1}. ^{1}H NMR (DMSO-d$_6$): δ 3.21 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.39 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.72 (2H, s, CH_2), 4.82 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 5.72 (2H, s, OH), 6.42 (2H, d, *J* = 9.1 Hz, ArH), 7.18-7.47 (14H, m, ArH), 7.62-7.75 (8H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 36.2, 40.7, 54.2, 115.1, 123.6, 124.9, 125.2, 126.9, 127.3, 128.0, 128.9, 129.2, 130.0, 131.6, 133.7, 135.2, 138.2, 152.9, 154.0, 170.1; MS: m/z (%) 674 (67, M^+), 570 (24), 466 (100), 104 (5), 77 (42).

4.2.2. 2-[4-(4-Bromophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-{3-[4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-hydroxybenzyl}phenol (4b). Brown solid; m.p. 191-193°C; IR (KBr): *v* 3444, 3061, 1680, 1572, 1449, 1410, 762 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.22 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.26 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.72 (2H, s, CH_2), 4.91 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 5.69 (2H, s, OH), 6.51 (2H, d, *J* = 9.0 Hz, ArH), 7.21-7.30 (12H, m, ArH), 7.67 (4H, m, ArH), 8.00 (4H, d, *J* = 8.4 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 37.1, 40.6, 54.2, 115.1, 121.7, 123.5, 124.9, 125.2, 126.0, 127.2, 128.2, 129.7, 130.4, 131.4, 133.5, 135.1, 142.1, 152.9, 155.5, 170.1; MS: *m/z* (%) 832 (100, M^+), 650 (18), 468 (29), 182 (30), 155 (48).

4.2.3. 2-[4-(4-Chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-{3-[4-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-hydroxybenzyl}phenol (4c). Yellow solid; m.p. 172-174°C; IR (KBr): *v* 3387, 3100, 1680, 1567, 1442, 1407, 682 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.22 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.25 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.69 (2H, s, CH_2), 4.97 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 5.72 (2H, s, OH), 6.52 (2H, d, *J* = 8.7 Hz, ArH), 7.20-7.30 (12H, m, ArH), 7.52 (4H, m, ArH), 7.80 (4H, d, *J* = 9.1 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 36.1, 40.7, 55.1, 115.7, 123.6, 124.6, 125.2, 126.9, 127.4, 128.7, 128.9, 129.4, 130.6, 133.5, 134.6, 135.6, 140.1, 52.5, 154.9, 169.4; MS: *m/z* (%) 744 (90, M^+), 606 (22), 469 (71), 138 (100), 111 (6).

4.2.4. 4-{4-Hydroxy-3-[4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]benzyl}-2-[4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]phenol (4d). Yellow solid; m.p. 189-191°C; IR (KBr): *v* 3410, 3067, 1672, 1562, 1442, 1410, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.27 (2H, dd, J_{AB} = 12.6, J_{AX} = 11.2 Hz, H_A), 3.30 (2H, dd, J_{BX} = 5.2, J_{BA} = 12.6 Hz, H_B), 3.70 (2H, s, CH_2), 3.84 (6H, s, OCH_3), 4.86 (2H, dd, J_{XA} = 11.2, J_{XB} = 5.2 Hz, H_X), 5.89 (2H, s, OH), 6.53 (2H, d, *J* = 8.6 Hz, ArH), 6.92 (4H, d, *J* = 8.4 Hz, ArH), 7.17 (4H, d, *J* = 8.4 Hz, ArH), 7.19-7.31 (8H, m, ArH), 7.57 (4H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 36.2, 41.2, 54.3, 56.7, 113.7, 115.2, 123.6, 124.9, 125.1, 125.9, 126.7, 128.2, 129.2, 130.0, 133.7, 134.6, 135.5, 152.6, 154.1, 160.2, 170.1; MS: *m/z* (%) 734 (86, M^+), 596 (41), 458 (15), 128 (21), 91 (100).

4.2.5. 4-{4-Hydroxy-3-[4-(4-nitrophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]benzyl}-2-[4-(4-nitrophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]phenol (4e). Brown solid; m.p. 210-212 °C; IR (KBr): *v* 3402, 3042, 1672, 1566, 1482, 1410, 1347, 1281, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.28 (2H, dd, J_{AB} = 12.6, J_{AX} = 11.2 Hz, H_A), 3.39 (2H, dd, J_{BX} = 5.2, J_{BA} = 12.6 Hz, H_B), 3.72 (2H,

s, CH_2), 4.90 (2H, dd, J_{XA} = 11.2, J_{XB} = 5.2 Hz, H_X), 5.92 (2H, s, OH), 6.53 (2H, d, J = 8.7 Hz, ArH), 7.20-7.32 (8H, m, ArH), 7.62 (4H, m, ArH), 8.10 (4H, d, J = 8.4 Hz, ArH), 8.23 (4H, d, J = 8.4 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 37.1, 40.2, 54.3, 115.1, 123.4, 124.0, 124.9, 125.2, 126.4, 127.0, 128.6, 129.3, 131.0, 133.7, 135.2, 146.9, 147.8, 152.9, 154.3, 169.5; MS: *m/z* (%) 764 (86, M^+), 615 (41), 466 (100), 149 (24), 123 (20).

4.2.6. 2-[4-(2-Furyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-3-[4-(2-furyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-4-hydroxybenzylphenol (4f). Brown solid; m.p. 191-193°C; IR (KBr): *v* 3352, 3037, 1678, 1565, 1282, 1107, 1030, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.28 (2H, dd, J_{AB} = 12.6, J_{AX} = 11.2 Hz, H_A), 3.41 (2H, dd, J_{BX} = 5.2, J_{BA} = 12.6 Hz, H_B), 3.72 (2H, s, CH_2), 4.91 (2H, dd, J_{XA} = 11.2, J_{XB} = 5.2 Hz, H_X), 5.90 (2H, s, OH), 6.36 (2H, d, J = 3.9 Hz, ArH), 6.53 (2H, d, J = 8.6 Hz, ArH), 6.70 (2H, dd, J = 3.9, 1.8 Hz, ArH), 7.19-7.39 (8H, m, ArH), 7.62 (4H, m, ArH), 8.00 (2H, d, J = 1.8 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 35.2, 42.0, 51.7, 111.1, 114.8, 115.3, 124.2, 125.4, 125.0, 126.7, 127.1, 128.9, 129.2, 132.5, 134.5, 145.6, 148.7, 151.4, 152.7, 154.1; MS: *m/z* (%) 654 (90, M^+), 560 (21), 466 (10), 94 (100), 68 (4).

4.2.7. 4-{4-Hydroxy-3-[4-(2-pyridyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]benzyl}-2-[4-(2-pyridyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]phenol (4g). Brown solid; m.p. 172-174°C; IR (KBr): *v* 3410, 3067, 1674, 1592, 1462, 1470, 1410, 1282, 1105 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.27 (2H, dd, J_{AB} = 12.6, J_{AX} = 11.2 Hz, H_A), 3.40 (2H, dd, J_{BX} = 5.2, J_{BA} = 12.6 Hz, H_B), 3.72 (2H, s, CH_2), 4.91 (2H, dd, J_{XA} = 11.2, J_{XB} = 5.2 Hz, H_X), 5.92 (2H, s, OH), 6.52 (2H, d, J = 8.6 Hz, ArH), 6.91 (2H, dd, J = 7.6, 4.9 Hz, ArH), 7.26-7.42 (10H, m, ArH), 7.62 (6H, m, ArH), 8.51 (2H, d, J = 4.9 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 34.1, 42.0, 50.6, 114.7, 122.5, 123.4, 124.1, 125.4, 126.0, 126.9, 127.3, 128.7, 129.9, 133.5, 134.6, 136.7, 149.9, 152.3, 153.5, 161.0, 169.3; MS: *m/z* (%) 676 (100, M^+), 570 (10), 466 (21), 105 (6), 78 (18).

4.3. General procedure for the Synthesis of methylene-bis-benzofurano-[1,5]-benzothiazepines (5a-g):

To a stirred solution of **4** (1 mmol), anhy. potassium carbonate (3 mmol) and catalytic amount of KI in dry acetone (30 mL), was added a solution of α-bromoacetophenone (2 mmol) in dry acetone (20 mL), drop wise, at reflux temperature. Reflux was continued for 12 h. The reaction mixture was concentrated to dryness and then poured into ice-cold water and the solid was collected by filtration. The crude product was dissolved in 0.1 *N* ethanolic KOH (100 mL) and further refluxed for 18 h. The excess ethanol was then removed by distillation *in vacuo* and the reaction mixture was poured into ice-cold HCl. The separated solid was collected by filtration and purified by column chromatography, using petrol ether (60-80 °C) as eluent, to give pure products **5a-g**. All the products were characterized by IR, ^{1}H, ^{13}C NMR and Mass spectra.

4.3.1. 4-Phenyl-2-(3-phenyl-5-[3-phenyl-7-(4-phenyl-2,3-di-hydro-1,5-benzothiazepin-2-yl) benzo[*b*]furan-5-yl]methylbenzo[*b*]furan-7-yl)-2,3-dihydro-1,5-benzothiazepine (5a). Brown solid; m.p. 151-153°C; IR (KBr): *v* 3037, 1678, 1605, 1565, 1211, 1177, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.91 (2H, s, CH_2), 5.47 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.84 (2H, s, ArH), 7.19-7.35 (8H, m, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (10H, m, ArH), 7.78 (2H, s, ArH), 7.91 (4H, d, J = 8.1 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 36.4, 42.1, 56.2, 112.4, 115.4, 122.3, 124.7, 125.1, 125.9, 126.8, 127.1, 128.3, 128.8, 129.1, 130.3, 131.0, 131.3, 132.1, 133.5, 134.8, 138.4, 140.7, 145.2, 151.6, 153.4, 167.6; MS: *m/z* (%) 876 (71, M^++1), 771 (100), 667 (18), 637 (19), 533 (20).

4.3.2. 4-(4-Bromophenyl)-2-[5-(7-[4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-3-phenylbenzo[*b*]furan-5-ylmethyl)-3-phenylbenzo[*b*]furan-7-yl]-2,3-dihydro-1,5-benzothiazepine (5b). Brown solid; m.p. 184-186°C; IR (KBr): *v* 3061, 1680, 1572, 1449, 1211, 1165, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} =

5.1, J_{BA} = 12.7 Hz, H_B), 3.92 (2H, s, CH_2), 5.49 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.84 (2H, s, ArH), 7.19-7.35 (6H, m, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (10H, m, ArH), 7.78 (2H, s, ArH), 7.96 (4H, d, J = 8.3 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 36.4, 42.1, 56.2, 112.3, 115.3, 121.8, 122.4, 124.6, 125.1, 125.9, 126.8, 127.3, 128.0, 129.0, 130.0, 130.3, 131.0, 132.1, 133.4, 134.7, 139.7, 140.2, 145.2, 151.5, 153.3, 167.5; MS: *m/z* (%) 1032 (67, M^+), 850 (41), 716 (21), 668 (7), 534 (10).

4.3.3. 4-(4-Chlorophenyl)-2-[5-(7-[4-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-3-phenylbenzo[*b*]furan-5-ylmethyl)-3-phenylbenzo[*b*]furan-7-yl]-2,3-dihydro-1,5-benzothiazepine (5c). Yellow solid; m.p. 162-164°C, IR (KBr): *v* 3065, 1680, 1577, 1449, 1215, 1165, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.94 (2H, s, CH_2), 5.50 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.87 (2H, s, ArH), 7.19-7.35 (6H, m, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (10H, m, ArH), 7.71 (4H, d, J = 8.4 Hz, ArH), 7.78 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 36.4, 42.1, 56.2, 112.4, 115.0, 122.0, 124.8, 125.2, 125.8, 126.8, 127.2, 128.1, 128.3, 129.1, 130.1, 131.0, 132.0, 133.5, 133.7, 134.6, 139.1, 140.3, 145.2, 151.4, 153.5, 167.6; MS: *m/z* (%) 944 (80, M^+), 806 (51), 668 (6), 534 (11).

4.3.4. 4-(4-Methoxyphenyl)-2-[5-(7-[4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-3-phenylbenzo[*b*]furan-5-ylmethyl)-3-phenylbenzo[*b*]furan-7-yl]-2,3-dihydro-1,5-benzothiazepine (5d).Yellow solid; m.p. 184-186°C, IR (KBr): *v* 3065, 2972, 1680, 1575, 1450, 1215, 1165, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.81 (6H, s, OCH_3), 3.94 (2H, s, CH_2), 5.49 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.84 (2H, s, ArH), 6.91 (4H, d, J = 8.4 Hz, ArH), 7.10-7.35 (6H, m, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (10H, m, ArH), 7.78 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 36.4, 42.1, 54.2, 56.0, 112.0, 112.7, 115.4, 122.3, 124.7, 125.1, 125.3, 125.8, 126.8, 128.1, 129.1, 130.2, 131.0, 132.3, 133.5, 134.1, 134.8, 140.5, 145.2, 151.4, 153.4, 162.1, 167.5; MS: *m/z* (%) 937 (69, M^+ +1), 802 (100), 668 (2), 534 (11).

4.3.5. 4-(4-Nitrophenyl)-2-[5-(7-[4-(4-nitrophenyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-3-phenylbenzo[*b*]furan-5-yl-methyl)-3-phenylbenzo[*b*]furan-7-yl]-2,3-dihydro-1,5-benzothiazepine (5e). Red brown solid; m.p. 210-212°C, IR (KBr): *v* 3062, 2972, 1678, 1605, 1565, 1450, 1372, 1220 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.91 (2H, s, CH_2), 5.50 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.84 (2H, s, ArH), 7.21 (2H, s, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (10H, m, ArH), 7.78 (2H, s, ArH), 8.00 (4H, d, J = 8.4 Hz, ArH), 8.17 (4H, d, J = 8.4 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ36.4, 42.0, 55.8, 112.6, 115.2, 122.1, 122.7, 124.6, 125.0, 125.9, 126.5, 126.8, 128.2, 129.0, 130.3, 131.0, 132.1, 133.2, 134.6, 140.7, 145.2, 146.7, 149.0, 151.6, 153.7, 167.2; MS: *m/z* (%) 966 (100, M^+), 817 (21), 683 (29).

4.3.6. 4-(2-Furyl)-2-[5-(7-[4-(2-furyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]-3-phenylbenzo-[*b*]furan-5-ylmethyl)-3-phenylbenzo[*b*]furan-7-yl]-2,3-dihydro-1,5-benzothiazepine (5f). Brown solid; m.p. 215-217°C, IR (KBr): *v* 3067, 2964, 1682, 1572, 1450, 1210, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.91 (2H, s, CH_2), 5.50 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.47-6.57 (4H, m, ArH), 6.84 (2H, s, ArH), 7.19-7.35 (6H, m, ArH), 7.40-7.47 (6H, m, ArH), 7.55-7.65 (8H, m, ArH), 7.78 (2H, s, ArH), 8.00 (2H, d, J = 7.2 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 33.7, 42.0, 52.4, 110.3, 112.7, 114.6, 115.0, 122.3, 124.7, 125.3, 125.8, 126.8, 128.2, 129.1, 130.1, 131.0, 132.1, 133.3, 134.7, 137.6, 140.7, 144.1, 145.2, 147.5, 150.6, 150.9, 151.5, 152.9; MS: *m/z* (%) 730 (100, M^+), 636 (20), 542 (14).

4.3.7. 2-[3-Phenyl-5-(3-phenyl-7-[4-(2-pyridyl)-2,3-dihydro-1,5-benzothiazepin-2-yl]benzo-[*b*]furan-5-ylmethyl)benzo[*b*]furan-7-yl]-4-(2-pyridyl)-2,3-dihydro-1,5-benzothiazepine (5g). Black solid; m.p. 215-217°C; IR (KBr): *v* 3062, 2932, 1681, 1579, 1450, 1212, 1030 cm^{-1}; ^{1}H

NMR (DMSO-d_6): δ 3.31 (2H, dd, J_{AB} = 12.7, J_{AX} = 11.4 Hz, H_A), 3.62 (2H, dd, J_{BX} = 5.1, J_{BA} = 12.7 Hz, H_B), 3.92 (2H, s, CH_2), 5.49 (2H, dd, J_{XA} = 11.4, J_{XB} = 5.1 Hz, H_X), 6.84 (2H, s, ArH), 7.00 (2H, m, ArH), 7.19-7.35 (6H, m, ArH), 7.40-7.47 (8H, m, ArH), 7.55-7.65 (12H, m, ArH), 8.70 (2H, d, J = 6.3 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 33.5, 42.0, 52.5, 112.5, 115.4, 121.5, 122.0, 123.7, 125.0, 125.2, 125.8, 126.7, 128.1, 129.1, 130.1, 131.0, 132.4, 133.4, 134.7, 140.6, 145.2, 148.6, 150.1, 151.6, 162.1, 164.3; MS: *m/z* (%) 878 (84, M^+), 772 (10), 666 (25).

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