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SYNTHESIS, CHARACTERIZATION AND *IN VITRO* ANTICANCER EVALUATION OF BIS-[1,5]-BENZOTHIAZEPINES AGAINST HUMAN BREAST CANCER CELL LINE MCF-7

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ABSTRACT: Bis-[1,5]-benzothiazepines **(3a-i)** containing two 1,5-benzothiazepine nuclei in a single molecule were synthesized by cyclocondensation reaction of bis-chalcones **(1a-i)** with two equivalent of 2-aminobenzenethiol **(2)**. All the synthesized compounds were characterized by IR, ^{1}H NMR,^{13}C NMR and mass spectral analysis. Anticancer activity of the synthesized compounds against human breast cancer cell line MCF-7 was determined and the compound **(3c)** showed significant activity comparable to 5-fluorouracil.

INTRODUCTION: 1,5-Benzothiazepines are privileged seven membered nitrogen and sulfur containing heterocyclic ring compounds due to their extensive and significant pharmacological properties like antimicrobial [1], antifungal [2], antihypertensive [3], anticancer [4], antiarrhythmic [5], anti-inflammatory [6], coronary vasodilatory [7], anticonvulsant [8], CNS depressant [9], anti-HIV [10] etc. Number of different methods have been reported for the synthesis of 1,5-benzothiazepines [11].

Most commonly used method involves the reaction of 2-aminobenzenethiol with α, β-unsaturated carbonyl compounds i.e ketones or chalcones. Due to broad profile of biological activities and availability of different routes for synthesis of 1,5-benzothiazepines, there is huge scope for the synthesis of 1,5-benzothiazepines.

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Review of literature for the synthesis of 1,5-benzothiazepines reveals that, some research groups have reported synthesis and biological activities of bis-[1,5]-benzothiazepines using bis-chalcone intermediates [12]. In continuation of our research work on synthetic studies in 1,5-benzothiazepines, we have reported the synthesis and antibacterial study of bis-[1,5]-benzothiazepines [13]. Inspired with the antibacterial activity results and to know the effect of two 1,5-benzothiazepine nuclei against human breast cancer cell line MCF-7, we have extended this work and synthesized bis-[1,5]-benzothiazepines **(3a-i)** by cyclocodensation reaction of bis-chalcones with two equivalent of 2-aminobenzenethiol using piperidine catalyst.

All the synthesized compounds were tested *in vitro* for their anticancer activity against human breast cancer cell line MCF-7 using 5-flurouracil as standard drug and compound **(3c)** with *p*-methoxy substituent has showed significant anti-breast cancer activity against MCF-7 cell line. To determine the possible mode of action, molecular docking studies of compound **(3c)** was carried out

using crystal structure of the human CDK-7 and it shows various key interactions shown in **Fig. 1.**

MATERIALS AND METHODS: All reactions were carried out under air atmosphere in dried glass-ware. Infrared spectra were recorded on a Perkine Elmer FTIR spectrometer. The samples were examined as KBr discs 5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC (300 MHz for ^{1}H NMR and 75MHz for ^{13}C NMR) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Perkin Elmer SQ 300 vectro model. Melting points were determined on MEL-TEMP capillary melting point apparatus and are uncorrected. Precoated aluminium sheets (silica gel 60 F254, Merk Germany) were used for thin-layer chromatography (TLC) and spots were visualized under UV light. All other chemicals were obtained from local chemical suppliers and were used without further purification.

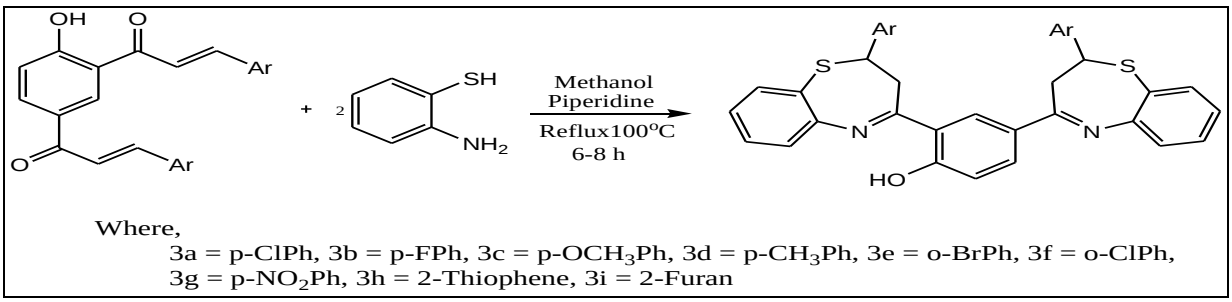
General procedure for the synthesis of bis-[1,5]-benzothiazepines (3a-i):

To a mixture of bis-chalcone (2 mmol) and 2-aminobenzenethiol (4 mmol) in methanol was added piperidine (20 mol%) and it was refluxed for 6-8 hours. After completion of the reaction as monitored by thin layer chromatography (TLC), the reaction mixture was left overnight at room temperature. The reaction mixture was poured in ice-water and solid obtained was filtered, washed with water and purified by column chromatography over silica gel using petroleum ether-ethyl acetate (80:20 v/v) to afford the pure compound.

RESULTS AND DISCUSSION: Bis-[1,5]-benzothiazepines **(3a-i)** incorporating two 1,5-benzothiazepine nuclei in a single molecule were synthesized **(Scheme 1)**. Bis-chalcone intermediates were prepared according to literature reported procedure[14]. Two α, β-unsaturated carbonyl groups at ortho and para position of –OH group in bis-chalcones **(1a-i)** were converted into 1,5-benzothiazepine rings by cyclocondensation reaction of bis-chalcones **(1a-i)** (2 mmol) with 2-aminobenzenethiol **(1)** (4 mmol) using piperidine catalyst. Formation of desired compounds **(3a-i)** were confirmed by IR, ^{1}H NMR,^{13}C NMR, mass and elemental analysis. IR spectrum of compound (**3a)** displayed band at 3448 cm^{-1} for –OH stretching of phenolic ring, band at 1599 cm^{-1} for C=N stretching and band at 821, 756 cm^{-1} for C-S stretching clearly reflecting the formation the formation of desired product.

Presence of two 1,5-benzothiazepine rings, one at ortho and second at para position of –OH group in phenol was clearly indicated by the ^{1}H NMR spectra, for example, in ^{1}H NMR spectrum of compound (3h) 1,5-benzothiazepine ring at para position of –OH in phenol displayed two doublet of doublet peaks for methylene and methine protons at δ 3.12 and δ 5.32 whereas 1,5-benzothiazepine ring at ortho position of –OH in phenol displayed two doublet of doublet peaks for methylene and methine protons at δ 3.57 and δ 5.48. Deshielding effect of –OH group causes downfield signals of methylene and methine protons of ortho-1,5-benzothiazepine ring, aromatic protons appears as multiplet in the region δ 6.60-8.04.

^{13}C NMR spectrum of same compound displayed separate peaks for methylene and methine carbons for two 1,5-benzothiazepine rings. 1,5-Benzothiazepine ring para to –OH group displayed peak at δ 37.58 and δ 55.46 for methylene and methine carbons whereas 1,5-benzothiazepine ring ortho to –OH group displayed peaks at δ 38.54 and δ 55.55 for methylene and methine carbons. Mass spectrum of the same compound displayed molecular ion peak at m/z = 580, which is in good agreement with the proposed structure.



Where,
3a = p-ClPh, 3b = p-FPh, 3c = p-OCH_3Ph, 3d = p-CH_3Ph, 3e = o-BrPh, 3f = o-ClPh, 3g = p-NO_2Ph, 3h = 2-Thiophene, 3i = 2-Furan

SCHEME 1: SYNTHESIS OF BIS-[1,5]-BENZOTHIAZEPINES

TABLE 1: PHYSICAL DATA OF BIS-[1,5]-BENZOTHIAZEPINES [a]

Entry	Ar	Product[b]	Time (h)	Obs. M.P (^oC)	Yield[c] (%)
1	*p*-ClPh	3a	5	140-142	84
2	*p*-FPh	3b	6	142-144	86
3	*p*-OCH_3Ph	3c	5	140-142	82
4	*p*-CH_3Ph	3d	5	152-154	84
5	*p*-BrPh	3e	7	136-138	76
6	*o*-ClPh	3f	5	144-146	84
7	*p*-NO_2Ph	3g	8	130-132	68
8	2-Thiophene	3h	7	170-172	82
9	2-Furan	3i	8	164-166	84

[a]Bis-chalcones (2 mmol), 2-aminobenzenethiol (4 mmol), Piperidine (20 mol %), methanol (20 ml) were refluxed at a temperature of 90^{o}C.
[b]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.
[c]Isolated yields after chromatography.

Anticancer activity:

Cell culture: MCF (human cervical carcinoma) cell lines were obtained from National Centre for Cell Sciences (NCCS), Pune, India, and were grown and maintained in MEM media and were grown and subcultured in medium supplemented with 10% fetal bovine serum, 1% L-Glutamine, 1% penicillin streptomyci-streptomycin-amphotericinc-B antibiotic solution. All cells were trypsinated using trypsin-EDTA solution and seeded in 96 well plates.

Cytotoxicity assay by MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide) assay method: The newly synthesized compounds were evaluated for their *in vitro* cytotoxic effects against MCF-7 (breast cancer cell line), by the standard MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide) assay using 5-FU (5-fluorouracil) as a positive control. The MCF-7 cell line was maintained in MEM medium supplemented with 10% fetal bovine serum. The cells were plated at a density of $1x10^5$ cells per well in a 96 well plate, and cultured for 24 h at 37^{o}C. The cells were subsequently exposed to 10 µM. The plates were incubated for 48 h, and cell proliferation was measured by adding 10 µL of MTT (thiazolyl blue tetrazolium bromide) dye (5 mg/ml in phosphate-buffered saline) per well. The plates were incubated for a further 4 h at 37^{o}C in a humidified chamber containing 5% CO_2. Formazan crystals formed due to reduction of dye by viable cells in each well were dissolved in 200 µl DMSO, and absorbance was read at 490 nm. The results were compared with the standard drug inhibition 5-flurouracil (10 µM). Percent cytotoxicity of the compound was calculated by using the formula

Percent Cytotoxicity = Reading of control – Reading of treated cells/Reading of control x 100

Inhibitory effects of compounds (3a-i) on the proliferation of MCF-7 cancer cell line: To evaluate the anticancer potential of the synthesized compounds, we tested *in vitro* anti-proliferative activities of compounds **(3a-i)** against human breast cancer cell line MCF-7 by employing MTT (3-(4, 5-dimethylthiazol-2-yl) 2, 5-diphenyl tetrazolium bromide) assay method. The results are described in **Table 2**. Notably, the compound **3c** exhibited significant inhibitory activitiy against MCF-7 cell lines with 74.78 % growth inhibition at 20 µM/mL concentration to the positive control 5-flurouracil.

TABLE 2: ANTICANCER ACTIVITY OF SYNTHESIZED COMPOUNDS (3a-i) AGAINST MCF-7 CELL LINE.

Compound	% Inhibition (20 µM)
3a	NA
3b	NA
3c	74.78
3d	NA
3e	NA
3f	NA
3g	NA
3h	NA
3i	NA
5-flurouracil	29.11

(NA = No activity)

Molecular docking studies: The master regulators, cyclin dependent kinases (CDK_S), have significant contribution in cancer which makes them promising target for novel therapeutic interventions. To ascertain the mode of action of the synthesized metal complexes molecular docking calculations are carried out using BIOPREDICTA module of the V life MDS 4.3. Virtual analysis was carried out using crystal

structure of the Human CDK 7 (pdb ID: IUA2) downloaded from Protein Data Bank (www.rcsb.org/pdb) at a resolution of 3.02 Å. Protein structure was refined via deletion of all the hetero atoms including water Molecules and addition of the polar hydrogen atoms to get a native conformation. The molecules **(3C)** was docked into the similar site showing various key interactions. 2,4-bis(*E*)-2,3-dihydro-2-(4-methoxyphenyl) benzo [b][1,4]thiazepine-4-yl)phenol **(3c)** showed hydrogen bond interaction with MET94 , aromatic interaction with PHE93 and hydrophobic interactions with LYS41, PHE91, THR96 and Van de Waals interaction with LEU18, GLY21, ALA39 **(Fig. 1)**.

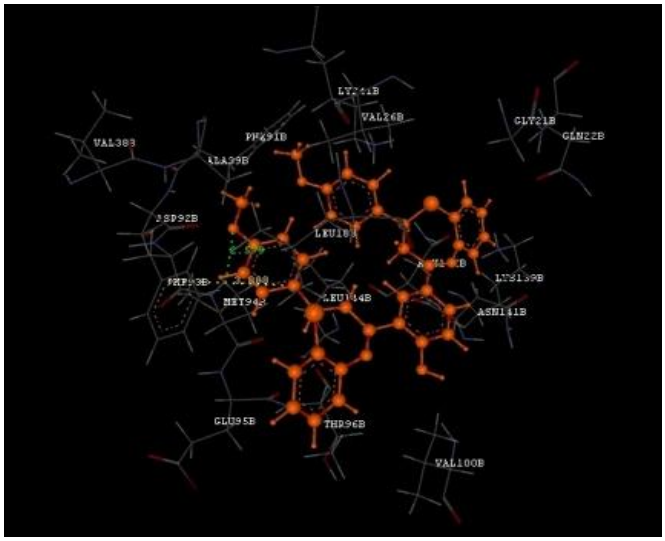


FIG.1: BINDING INTERACTION OF MOLECULE (3C) WITH CDK 7

Spectral data of representative compounds:

2,4-bis(E)-2-(4-chlorophenyl)-2,3-dihydro benzo [b][1,4]thiazepin-4-yl)phenol (3a): Yellow solid, mp- 140-142^{o}C; FTIR (KBr, thin film): **ν** = 3448 (Ar-OH), 1599 (C=N), 756 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13 (dd, 2H, CH_2, J = 12.24 Hz, 5.1 Hz), 3.47 (dd, 2H, CH_2, J= 5.13 Hz, 8.49 Hz), 4.93 (dd, 1H, CH, J = 4.95 Hz, 4.92 Hz), 5.10 (dd, 1H, CH, J = 4.17, 4.89 Hz), 6.54-8.39 (m, 19H, Ar-H), 15.02 (s, 1H, Ar-OH); ^{13}C NMR ($CDCl_3$): δ 167.0, 161.6, 159.4, 148.0, 144.1, 135.3, 135.2, 133.7, 130.4, 130.2, 129.9, 129.3, 127.7, 126.8,126.6, 125.0, 118.9, 118.6, 118.0, 114.4, 114.1, 60.0, 55.4, 55.3, 39.0, 37.3; Mass (EI) m/z = 639 (M+2); Anal. Calcd. for $C_{36}H_{26}Cl_2N_2OS_2$: %C 67.81, %H 4.11, %N 4.39, Observed: %C 67.84, %H 4.13, %N 4.43

2,4-bis(E)-2-(4-flurophenyl)- 2, 3 dihydrobenzo [b] [1,4]thiazepin-4-yl)phenol (3b): Yellow solid, mp: 142-144^{o}C; FTIR (KBr, thin film): ν = 3070 (Ar-OH), 1606, 1597 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.07 (dd, 2H, CH_2, J= 11.7 Hz, 4.5 Hz), 3.51 (dd, 2H, CH_2, J=10.5 Hz, 3.6 Hz), 5.00 (dd, 1H, CH, J= 5.1 Hz, 6.3 Hz), 5.15 (dd, 1H, CH, J= 5.1 Hz, 6.6 Hz), 6.66-7.70 (m, 19 H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 148.9, 148.3, 136.9, 135, 2, 131.7, 130.1, 129.8, 129.5, 127.8, 126.7, 125.6, 125.2, 118.6, 118.4, 117.83, 115.8, 115.5, 111.3, 77.4, 77.0, 76.5, 55.4, 55.7, 39.98, 39.70 ppm; Mass (EI) m/z = 605 (M+1); Anal. Calcd. for $C_{36}H_{26}F_2N_2OS_2$: C 71.50, H 4.33, N 4.63, Observed: C 71.54, H 4.36, N 4.67.

2,4-bis(E)-2,3- dihydro - 2 - (4-methoxyphenyl) benzo[b][1,4]thiazepine-4-yl)phenol (3c): Yellow solid, mp- 176-178 ^{o}C; FTIR (KBr, thin film): **ν** = 3448 (Ar-OH), 1599, 1510 (C=N), 1250, 1212 (-OCH_3), 756, 629 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.12 (dd, 2H, CH_2, J=11.7, 11.7 Hz), 3.49 (dd, 2H, CH_2, J= 4.8, 4.8 Hz), 3.78 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.96 (dd, 1H, CH, J=4.8, 5.5 Hz), 5.18 (dd, 1H, CH, J=4.8, 5.7 Hz), 6.83-8.35 (m, 19H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 148.5, 141.3, 135.2, 134.9, 134.0, 133.4, 132.4, 130.8, 130.1, 129.9, 129.5, 129.0, 128.9, 128.4, 128.0, 127.5, 126.9, 126.8, 125.6, 125.1, 118.6, 118.1, 77.4, 76.5, 59.6, 59.4, 54.7, 54.4, 39.9, 39.7 ppm; Mass (EI) m/z = 629 (M+1); Anal. Calcd. for $C_{38}H_{32}N_2O_3S_2$: %C 72.58, %H 5.13, %N 4.46, Observed: %C 72.61, %H 5.17, %N 4.49.

2,4-bis((E)-2,3-dihydro-2-p-tolylbenzo [b] [1,4] thiazepin -4-yl) phenol (3d): Yellow solid, mp: 152-154^{o}C; FTIR (KBr, thin film): **ν** = 3446 (Ar-OH), 1607, 1597 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H, CH_3), 2.42 (s, 3H, CH_3)**,** 3.10 (dd, 2H, CH_2, J= 11.34 Hz, 3.64 Hz), 3.61 (dd, 2H, CH_2, J=6.29 Hz, 4.51 Hz), 5.07 (dd, 1H, CH, J= 7.72 Hz, 7.82 Hz), 5.34 (dd, 1H, CH, J= 8.54 Hz, 5.86 Hz), 6.49-7.29 (m, 19 H, Ar-H), 15.17 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 148.7, 148.5, 137.6, 135, 5, 132.1, 130.9, 129.3, 129.0, 127.4, 126.7, 126.2, 122.7, 118.1, 117.9, 117.8, 115.9, 115.2, 113.5, 77.6, 77.2, 76.7, 54.9, 54.5, 38.12, 37.79, 28.41, 28.03 ppm; Mass (EI) m/z = 598 (M+1); Anal. Calcd. For $C_{38}H_{32}N_2OS_2$: %C 76.48, %H 5.40, %N 4.69, Observed: %C 76.42, %H 5.35, %N 4.62

2,4-bis((*E*)-2-(4-bromophenyl) - 2, 3 - dihydro benzo[b] [1,4]-thiazepin-4-yl)phenol (3e): Yellow solid, mp- 136-138^{o}C; FTIR (KBr, thin film): ν = 3147 (Ar-OH), 1604, 1579 (C=N), 752, 621 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04 (dd, 2H, CH_2, J=11.52 Hz, 3.36 Hz), 3.47 (dd, 2H, CH_2, J= 5.19 Hz, 4.11 Hz), 5.02 (dd, 1H, CH, J=7.77 Hz , 7.8 Hz), 5.13 (dd, 1H, CH, J= 7.77 Hz , 5.43 Hz), 6.58-7.16 (m, 19H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 148.4, 147.9, 141.4, 135.7, 134.5, 133.6, 132.1, 130.4, 129.3, 129.2, 128.8, 128.5, 128.3, 129.9, 127.8, 126.2, 126.1, 125.2, 125.1, 118.9, 118.4, 77.9, 77.4, 60.7, 59.7, 52.5, 51.7, 40.4, 40.1 ppm; Mass (EI) m/z = 728 (M+2); Anal. Calcd. For $C_{36}H_{26}Br_2N_2OS_2$; %C 59.51, %H 3.61, %N 3.86, Observed: %C 59.47, %H 3.57, %N 3.80

2,4-bis-((*E*)-2-(2-Chlorophenyl) - 2, 3 - dihydro benzo[b][1,4]thiazepin-4-yl) phenol (3f): Yellow solid, mp- 144-146^{o}C; FTIR (KBr, thin film): ν = 3124 (Ar-OH), 1607, 1589 (C=N), 630, 627 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.33 (dd, 2H, CH_2, J=11.9 Hz, 11.7 Hz), 3.56 (dd, 2H, CH_2, J= 4.7 Hz, 4.7 Hz), 4. 87 (dd, 1H, CH, J=4.8 Hz , 6.3 Hz), 5.12 (dd, 1H, CH, J=4.8 Hz , 6.4 Hz), 6.74-8.48 (m, 19H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 148.4, 142.2, 135.7, 134.7, 134.3, 133.8, 132.7, 131.3, 130.4, 130.2, 129.7, 129.4, 128.2, 128.1, 127.7, 127.2, 126.7, 126.1, 125.5, 125.4, 118.9, 118.7, 77.6, 77.2, 52.2, 51.5, 39.3, 38.2 ppm; Mass (EI) m/z = 639 (M+2); Anal. Calcd. For $C_{36}H_{26}Cl_2N_2OS_2$: %C 67.81, %H 4.11, %N 4.39, Observed: %C 67.76, %H 4.06, %N 4.33

2,4-bis((*E*)-2,3-dihydro-2-(4-nitrophenyl) benzo [b] [1,4]thiazepin-4-yl)phenol (3g): Yellow solid, mp: 130-132^{o}C; FTIR (KBr, thin film : ν = 3341 (Ar-OH), 1603 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (dd, 2H, CH_2, J= 11.64 Hz, 4.31 Hz), 3.63 (dd, 2H, CH_2, J=5.14 Hz, 4.11 Hz), 5.11 (dd, 1H, CH, J= 7.7 Hz, 7.8 Hz), 5.24 (dd, 1H, CH, J= 7.47 Hz, 4.83 Hz), 6.47-8.06 (m, 19 H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.6, 148.5, 148.1, 136.8, 136, 3, 132.4, 130.7, 129.6, 129.3, 127.4, 126.3, 126.1, 125.6, 118.9, 118.7, 117.3, 116.2, 115.3, 115.1, 77.6, 77.1, 54.4, 54.1, 39.42, 38.95 ppm; Mass (EI) m/z = 659 (M+1); Anal. Calcd. for $C_{36}H_{26}N_4O_5S_2$; %C 65.64, %H 3.98, %N 8.51, Observed: %C 65.57, %H 3.93, %N 8.46

2,4-bis(E)-2,3-dihydro - 2 - (thiophen-2-yl) benzo [b][1,4]thiazepin-4-yl)phenol (3h): Yellow solid, mp: 170-172^{o}C; FTIR (KBr,thin film): ν = 3362 (Ar-OH), 1606, 1558 (C=N), 688, 662 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.09 (dd, 2H, CH_2, J=11.4 Hz, 11.7 Hz), 3.57 (dd, 2H, CH_2, J= 4.8 Hz, 7.2 Hz), 5.32 (dd, 1H, CH, J= 3 Hz, 9.3 Hz), 5.48 (dd, 1H, CH, J= 5.7 Hz, 6.3 Hz), 6.60-8.04 (m, 17H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.3, 148.6, 148.1, 136.8, 135.7, 135.7, 133.9, 132.1, 131.6, 130.4, 129.8, 128.7, 128.4, 126.9, 126.8, 126.5, 125.4, 125.3, 124.8, 124.5, 124.2, 124.1, 123.9, 118.7, 118.6, 117.9, 55.5, 55.4, 38.5, 37.5 ppm; Mass (EI) m/z = 580 (M^+); Anal. Calcd. For $C_{32}H_{24}N_2OS_4$: %C 66.17,% H 4.17,% N 4.82, Observed:% C 66.20, %H 4.21, %N 4.84

2,4-bis(E)-2-(furan-2-yl)-2,3-dihydro benzo [b] [1,4] thiazepine-4-yl)phenol (3i): Yellow solid, mp: 164-166^{o}C; FTIR (KBr, thin film): ν =3362 (Ar-OH), 1606, 1558 (C=N), 688, 662 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.09 (dd, 2H, CH_2, J=12.3 Hz, 11.7 Hz), 3.59 (dd, 2H, CH_2, J= 9.3 Hz, 13.2 Hz), 4.14 (dd, 1H, CH, J = 6.9 Hz, 7.2 Hz), 5.44 (dd, CH, J = 4.8 Hz, 4.5 Hz), 6.60-8.25 (m, 17H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6, 147.6, 146.9, 146.1, 136.8, 135.4, 132.7,131.4,130.5, 130.2, 128.6, 128.2, 126.5, 126.1, 125.3, 125.1, 124.9, 124.7, 124.4, 124.2, 118.9, 118.3, 116.9, 116.2, 54.45, 54.36, 37.34, 37.20 ppm; Mass (EI) m/z = 548 (M^+); Anal. Calcd. For $C_{32}H_{24}N_2O_3S_2$: %C 70.05, %H 4.41, %N 5.51, Observed: %C 70.09, %H 4.45, %N 5.54.

CONCLUSION: In summary, we have synthesized and fully characterized bis-[1,5]-benzothiazepines (3a-i) by cyclocondensation of bis-chalcones with 2-aminobenzenethiol using piperidine catalyst in good yield. Anticancer evaluation of synthesized compounds showed that *p*-methoxy derivative (3c) exhibited significant activity against human breast cancer cell line MCF-7. Thus, the promising activity exhibited by *p*-methoxy derivative and easy access of bis-[1,5]-benzothiazepines render them as attractive anticancer agents. The extensive study of the SAR of this series of compounds will provide information for the design and development of new anticancer drugs based on bis-[1,5]-benzothiazepine derivatives.

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