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A Facile Synthesis, Characterization and Anticancer Activity Evaluation of Benzothiazole Derivatives

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KEYWORDS

Benzothiazole derivatives, Cell culture, MTT assay

ABSTRACT:

In this work novel organic based compound, Four new Benzothiazole derivatives were synthesized. The structures of the synthesized compounds were elucidated using UV,FT-IR,1H-NMR,13C-NMR, liquid chromatogram and mass spectral data. Anticancer activity of the compounds BZ-I,BZ-II,BZ-III and BZ-IV against MCF-7(human breast cancer cell line) was evaluated by using MTT assay. Cell culture studies have demonstrated significant toxicity of the compounds on the cell lines and their percentage cell viability were found. These results confirm the novel Benzothiazole derivatives may be utilized for breast cancer treatment. Furthermore, these compounds have a great potential and significance for further investigations.

Introduction

Synthesis of different types of benzothiazole derivatives such as was achieved through various process or methods including diazo-coupling, Knoevenagel condensation, Biginelli reactions ,Molecular hybridization techniques,microwave irradiation, onepot multi component reaction. Benzothiazole (BTA) represents a of sulphur containing heterocyclic compounds comprising a benzene ring fused with a thiazole ring. It finds immense applications as phyto hormones, antioxidants, enzyme inhibitors etc[1-5].Notably, a benzothiazole plays a key role in medicinal chemistry providing a substantial range of compounds pertaining to anti bacterial [6-8] antimicrobial,[9-13]anticancer,[14-17]enzyme inhibitor[18,19]. As such the synthesis and derivation of Benzothiazole unique moiety are quite paramount due to its diverse application in clinical and industrial domains. Cancer is spreading worldwide and is one of the leading causes of the death. The existing chemotherapeutic agents is commonly limited due to adverse effects. In this context wee used an electrochemical method to create a series of sulphur linked Benzothiazole derivatives and explored their anticancer potential. The biological profile of the synthesized lines[20] structure – activity relationships derived using their cell type has revealed that activity follows the heterocyclic sequence. Benzothiazole > benzoxazole>> benzimidazole and that Benzothiazole derivatives are especially potent and their activity extends to ovarian, lungs and renal cell lines[21]. Substituted Benzothiazole and its derivatives have received considerable attention for past last two decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. A literature survey indicates that Benzothiazole derivative process different pharmological and biological activities. Which of most potent activity are anticancer, antibacterial and antifungal activity[22]. The synthesized BTA derivatives were characterized by UV,FT-IR,^{1}H-NMR,^{13}C-NMR and mass spectra.

Materials and methods:

a)Synthesis of N-(1,3-benzothiazol-2-yl)-2-[4-(furan-2-carbonyl)piperazin-1-yl] acetamide. (BZ-I)

To the mixture of N-(1,3-benzothiazol-2-yl)-2-chloroacetamide (1g, 0.0044 mol) (BTCA) and 1-(2-furoyl)piperazine (0.864, 0.0048 mol) in

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Dimethylformamide potassium carbonate (1.52 g, 0.011 mol) was added. The resulting reaction mixture was heated at 70^0C for 8 h. The process of the reaction is monitored by TLC using chloroform : methanol (9.5: 0.5). The reaction mixture was cooled and filtered. To the filtrate, water (100 mL) was added and extracted with ethyl acetate (2x150 mL). The combined ethyl acetate was washed with brine solution (1x200 mL), dried on sodium sulfate and concentrated under reduced pressure. The resulting product was purified and recrystallized in ethanol.**Scheme-1** Pale yellow solid; Yield 88%;

b) Synthesis of N-(1,3 Benzothiazole -2-yl)-2-[4-Pyridin-2-yl)piperazin-1-yl]acetamide (BZ-II)

To the mixture of BTCA (1.25g,0.0055 mol), 2-(1-piperazinyl) pyridine (0.99g,0.006 mol) in acetonitrile, potassium carbonate (2.28g ,0.016mol) was added. The resulting reaction mixture was heated at 75^0C for 4 h. The reaction was cooled . The filtrate was concentrated, diluted with 150 mL of water and extracted with ethyl acetate (2x150 mL) and concentrated under reduced pressure. The resulting product was recrystallized from ethanol. **Scheme-1I** Light brown solid; Yield 85%.

c) Synthesis of N-(-2-yl)-2-[41,3-benzothiazol-(pyridine-2-carbonyl)piperazin-1-yl]acetamide (BZ-III)

To the mixture of BTCA (1g, 0.0044 mol) and (piperazin-1-yl)(pyridin-2-yl)methanone (0.92, 0.0048 mol) in Acetonitrile, potassium carbonate (2.13g, 0.015 mol) was added. The resulting reaction mixture was heated at 75^0C for 12 h. The reaction mixture filtered and concentrated. The resulting crude product was portioned between 150 mL of water and ethyl acetate (150 mL). The ethyl acetate layer was washed with brine solution (1x200 mL), dried on sodium sulfate and concentrated under reduced pressure. The resulting product was recrystallized from ethanol. **Scheme-1II** Pale yellow solid; Yield 86%

d) Synthesis of N-(1,3-benzothiazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide (BZ-IV)

To the mixture of N-(1,3-benzothiazol-2-yl)-2-chloroacetamide (1.2 g, 0.0053 mol) and N-methyl piperizine (0.64 ml, 0.0058 mol) in DMF, potassium carbonate (2.19g, 0.015 mol) was added. The resulting reaction mixture was heated at 80^0C for 5 h. The reaction mixture filtered and concentrated. The resulting crude product was portioned between 200 mL of water and ethyl acetate (250 mL). The ethyl acetate layer was washed with brine solution (1x250 mL), dried on sodium sulfate and concentrated under reduced pressure. The resulting product was washed with diethyl ether to afford pure product. **Scheme-1V** Pale yellow solid; Yield 88%;

Sample preparation:

About 1 mg of each sample was weighed and dissolved in a (Dulbecco's modified Eagle's medium) DMEM medium and serially diluted to attain the desired concentration for cell viability using MTT analysis.

Cell culture:

The human breast cancer cell line (MCF-7) was obtained from the National Centre for Cell Science (NCCS) in Pune and cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS). All cells were kept at 37°C, 100% relative humidity, 5% CO2, and 95% air, with the culture medium changing twice a week.

Cell treatment:

Trypsin-ethylenediaminetetraacetic acid (EDTA) was used to detach the monolayer cells and generate single-cell suspensions. A hemocytometer was used to count the viable cells, and the cell suspension was diluted with 5% FBS medium to achieve a final density of $1x10^5$ cells/ml. 96-well plates were seeded with one hundred microlitres of cell suspension per well and incubated for cell attachment at 37° C, 5% CO2, 95% air, and 100% relative humidity. After 24 hours, the cells were treated with different concentrations of the test samples (512 - 1 µg/ml). The serial dilution method was used to prepare test samples of various concentrations. By adding aliquots of 100 µl of the various drug dilutions to the appropriate wells already containing 100 µl of a medium, the required final drug concentrations of 512-1 g/ml were obtained. After the treatment of cells with test drug, the plates were incubated for another 24 -48 hours at 37° C, 5% CO2,

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95% air, and 100% relative humidity. The medium without test drug/no drug served as a control and all concentrations were run in triplicate.

MTT Assay:

After 24 - 48 hours, the medium containing the drug was aspirated, and 10-15 µl of MTT (5mg/ml) in phosphate-buffered saline (PBS) was added to each well and incubated at 37° C for 4 hours. The MTT medium was removed, and the formed formazan crystals were dissolved in 100 µl of DMSO. The absorbance was measured at 570 nm using a microplate reader. The percentage of cell viability was determined using the following formula.

% Cell viability = [Abs (sample)/Abs (control)] x100

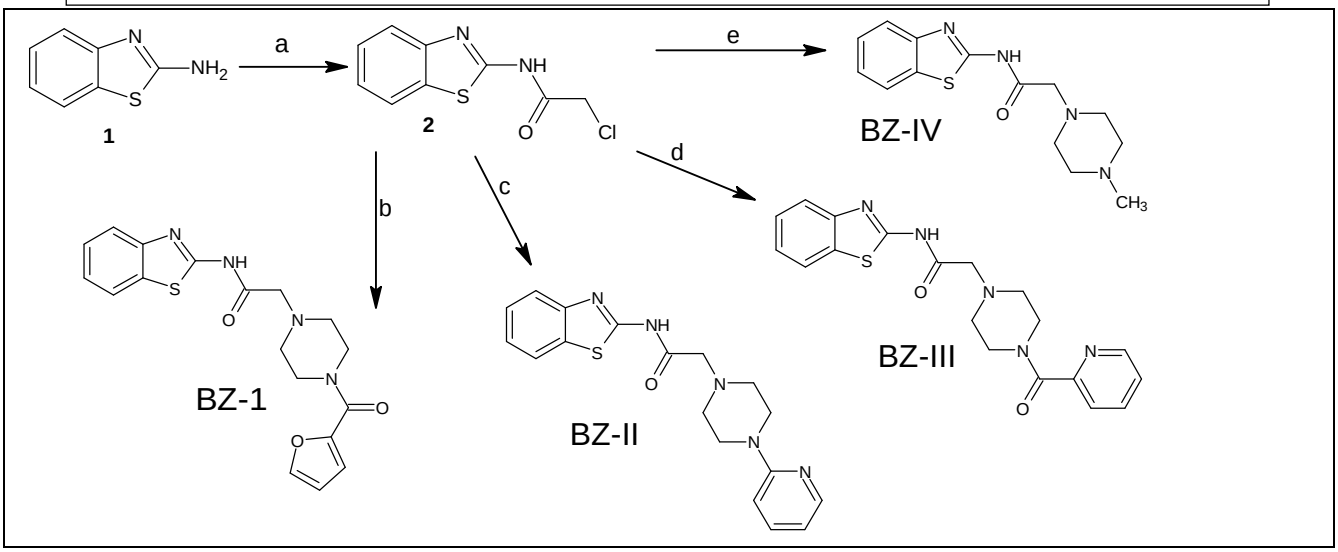

FIGURE-1 Scheme 1: BZ-I (a). Chloroacetyl chloride, DMF, K_2CO_3, 0˚C, 6h,

(b). 1-(2-furoyl)piperazine, DMF, K_2CO_3, 70˚C, 8h

Scheme 2: BZ-II (c). 2-(1-Piperazinyl) pyridine, ACN, K_2CO_3, 75˚C, 4h

Scheme 3: BZ-III (d). (piperazin-1-yl) (pyridin-2-yl) methanone ACN, K_2CO_3, 75˚C, 12h

Scheme 4:BZ-IV (e). N-methyl piperizine, DMF, K_2CO_3, 80˚C, 7h

Result and discussion

a) Characterization of N-(1,3-benzothiazol-2-yl)-2-[4-(furan-2-carbonyl)piperazin-1-yl]acetamide

The above key intermediate **2** was allowed to react with 1-(2-furoyl)piperazine to make the final compound **BZ-I**. The reaction was carried out in the presence of Potassium carbonate base in DMF.

The synthesized compound exhibited characteristic FT-IR C=O stretching frequency at 1606 cm^{-1}. The FT-IR spectrum of **BZ-I** showed the expected frequencies of NH, C-N and C-S at 3436 cm^{-1}, 1246 cm^{-1} and 720 cm^{-1}, respectively In the ^{1}H-NMR spectrum of **BZ-I**, the proton signal of NH recoded at δ 12.18 ppm as broad singlet. The eight piperazine ring protons were resonated at δ 2.62 ppm and δ 3.72 ppm as triplets. In ^{13}C-NMR spectra of **BZ-I**, the two characteristic C=O groups were resonated at δ 158.68 ppm and δ 169.75 ppm which confirmed the expected compound N-(1,3-

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benzothiazol-2-yl)-2-[4-(furan-2-carbonyl)piperazin-1-yl]acetamide. The mass spectrum of **BZ-I** showed a molecular ion peak at m/z 371 $(M+H)^+$

b) Characterization of N-(1,3-benzothiazol-2-yl)-2-[4-(pyridin-2-yl)piperazin-1-yl]acetamide

The FT-IR spectrum for BZ-II shows the appearance of the characteristic absorption bands at 1612 cm^{-1} due to C=O stretching frequency. The FT-IR spectrum also shows the appearance of absorption band in the region 3423 cm^{-1} due to the stretching vibration of the amide NH group. Furthermore, the compound BZ-II exhibited additional absorption bands at 2916 cm^{-1} and 2852 cm^{-1}, respectively, which corresponds to stretching of the aliphatic C-H bond. The ^{1}H NMR spectrum of BZ-II recorded in DMSO-d_6.The ^{1}H-NMR spectrum revealed the presence of four triplet of doublet pattern at δ 6.49, 6.67, 7.17 and 7.37 ppm due to the existence of expected aromatic protons. The characteristic peaks between δ 2.37 to δ 3.38 ppm were assigned to aliphatic protons present in the **BZ-II**. The ^{13}C NMR spectrum of BZ-II showed one downfield signal observed at δ 169.7 ppm is attributed to the carbonyl carbons of resulting synthesized compound However, the upfield signals at δ 44.8, 52.4 and 60.4 ppm is assigned for aliphatic carbons. The resonance due to the aromatic carbons are observed at δ 107.4, 113.2, 120.7, 121.9, 123.9, 126.4, 131.6, 137.8, 147.7, 148.5, 157.7 and 159.1 ppm. The mass spectrum showed a molecular ion peak at m/z 354.1 $(M+H)^+$

c) Characterization of N-(-2-yl)-2-[41,3-benzothiazol-(pyridine-2-carbonyl)piperazin-1-yl]acetamide

To the mixture of N-(1,3-benzothiazol-2-yl)-2-chloroacetamide and (piperazin-1-yl)(pyridin-2-yl) methanone (0.92, 0.0048 mol) in Acetonitrile, potassium carbonate was added.

The FT-IR spectrum of resulting compound showed absorption band at 3423 cm^{-1} due to new amide NH group and the characteristic stretching frequency of C=O stretch was observed at 1716 cm^{-1},3049 (CH stretch, aromatic), 2914, 2817 (CH stretch, aliphatic), 1548 (C=C stretch), 1439 (CH bend, aliphatic), 1252 (C-N stretch, amide), 956 (C-N stretch), 736 (C-S stretch); ^{1}H NMR (DMSO-d_6) δ ppm: 2.50 (t, 2H), 2.60 (t, 2H), 3.37 (t, 4H), 3.65 (s, 2H), 7.25 (t, 1H), 7.37-7.42 (m, 2H), 7.51 (d, 1H), 7.68 (d, 1H), 7.86 (t, 1H), 7.91 (d, 1H), 8.53 (d, 1H), 12.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm: 39.5, 44.5, 50.1, 50.6, 57.8, 118.5, 119.7, 121.1, 121.6, 122.5, 124.1, 129.4, 135.3, 146.3, 151.9, 155.4, 164.6, 167.3; LC-MS (ESI) m/z : 382.1 $(M+H)^+$

d) Characterization of N-(1,3-benzothiazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide

(BZ-IV)

The final compound N-(1,3-benzothiazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide was obtained by coupling reaction between N-(1,3-benzothiazol-2-yl)-2-chloroacetamide and N-methyl piperizine in DMF. The potassium carbonate was used as base for the reaction. The coupling product of resulting compound was confirmed by FT-IR, NMR and LC-MS. 3443 (NH stretch, Amide), 3049 (CH stretch, aromatic), 2933, 2831 (CH stretch, aliphatic), 1702 (C=O stretch), 1522 (C=C stretch), 1439 (CH bend, aliphatic), 1258 (C-N stretch, amide), 1116 (C-N stretch), 724 (C-S stretch); ^{1}H NMR (DMSO-d_6) δ ppm: 2.16 (s, 3H), 2.35 (t, 4H), 2.53 (t, 4H), 3.58 (s, 2H), 7.30 (t, 1H), 7.42 (t, 1H), 7.73 (d, 1H), 7.96 (d, 1H), 11.90 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 45.6, 52.4, 54.5, 60.1, 120.5, 121.7, 123.6, 126.1, 131.4, 148.4, 157.4, 169.4; LC-MS (ESI) m/z : 291.1 $(M+H)^+$.

MTT assay

The results of the MTT assay for the compounds BZ-I,BZ-II,BZ-III and BZ-IV weretested against MCF-7 cell lines for various concentrations and were shown in the Table- 1 represented below and figure 3. As the concentration increases there is an increase in the cell growth inhibition and it was found to be 39.18,40.62,29.22 and 22.34% growth inhibition at 512 µg/ml, for BZ-I,BZ-II,BZ-III and BZ-IV respectively. The IC50 value BZ-IV,BZ-III,BZ-I and BZ-II 51.97,77.811,234.575 and 267.401 µg/ml, shown in table-2 and figure-2 respectively.

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Table 1: Percentage of cell viability – MTT assay

		BZ-I	BZ-II	BZ-III	BZ-IV
S.No	**Concentrations**	**% of Vilability**	**% of Vilability**	**% of Vilability**	**% of Vilability**
1	512	39.184±1.630	40.622±1.471	29.229±4.18	22.345±1.864
2	256	48.655±1.506	49.217±2.221	37.061±1.338	32.615±0.962
3	128	57.899±1.584	27.426±1.669	42.849±0.935	39.105±2.185
4	64	62.775±0.553	63.986±1.856	50.988±1.493	49.892±0.821
5	32	69.984±1.732	70.590±0.860	60.504±0.895	58.004±0.766
6	16	74.466±1.216	75.834±1.383	68.318±0.716	62.539±0.886
7	8	84.131±1.300	79.421±0.491	77.562±1.168	69.634±1.682
8	4	88.797±1.472	86.771±1.576	85.183±1.201	80.333±1.346
9	2	94.269±1.547	90.349±1.184	88.516±1.106	86.525±0.749
10	1	96.909±1.123	93.489±0.922	92.191±0.463	91.314±2.319

Table-2 IC50 Value

S.No	**Sample**	**IC50 Value**
1	BZ-I	234.575
2	BZ-II	267.401
3	BZ-III	77.811
4	BZ-IV	51.97

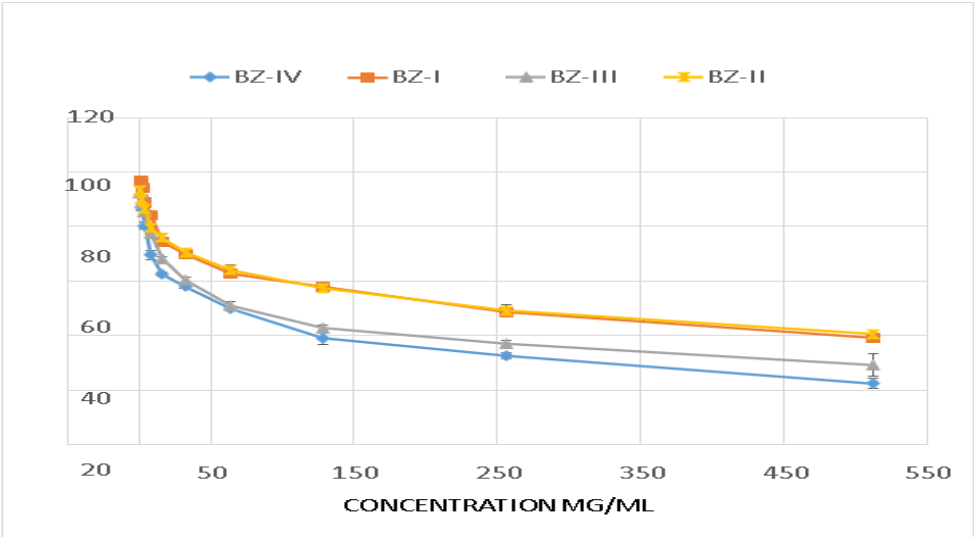

Figure-2 ANTICANCER ACTIVITY AGAINST MCF-7 HUMAN BREASTCANCER CELL LINE

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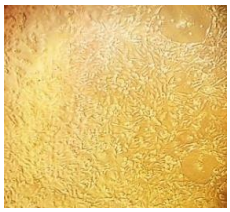
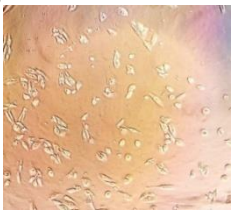
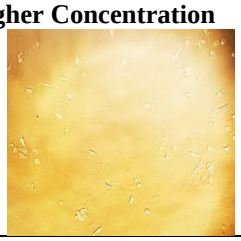
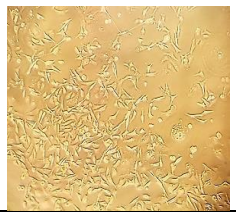
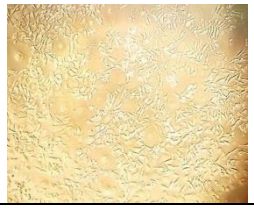
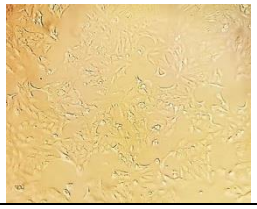
Figure-3 MTT ASSAY :

BZ-I	 **Higher Concentration**	 **Lower concentration**
BZ-II	**Higher Concentration** 	 **Lower concentration**
BZ-III	 **Higher Concentration**	 **Lower concentration**
BZ-IV	**Higher Concentration** 	**Lower concentration** 
CONTROL		

Conclusion

The present work reported the synthesis, characterization and anticancer activity of four benzothiozole derivatives such as BZ-I,BZ-II,BZ-III and BZ-IV. Their structural details were analysed by several spectroscopic tools. Numerous outstanding achievements revealed that Benzothiazole derivatives possess extensively potential application as medicinal drugs and diagnostic agents. There are much scope in this moiety as a numerous molecular targets in future

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investigations of this scaffold could give numerous results in medicinal fields.

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Conflict of interest

The authors declare no conflict of interests regarding the publication of this article.

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