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BENZOTHIAZEPINE HYBRIDS AS PROMISING ANTIOXIDANT AND ANTI-CANCER AGENTS: DESIGN, SYNTHESIS, MOLECULAR DOCKING AND *IN VITRO* STUDIES

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ABSTRACT

Novel benzothiazepines were designed and subjected for molecular docking study and the compounds possess significant interaction with the targeted enzyme topoisomerase II. Among them compound BD3and BD6 (-7.9kcal/mol) showed similar docking compared to Adriamycin (-12.76kcal/mol). Based on the experimental results, among all the compounds synthesized, compound BD1 substituted with acetaldehyde showed good inhibition (127.02µg/mL). The *in-vitro* cytotoxic evaluation was carried out for the synthesised compounds and the results were found that the synthesized compounds are relatively non-toxic at 100µg concentration in tested cell line. Among the tested compounds, compound BD3 substituted with methyl benzene group were found to have IC_{50} values 46.4023µg/mL against MCF – 7 cancer cell lines. Compound BD6 substituted with chloro-benzene were found to have IC_{50} values 95.8213µg/mL against MCF7 cancer cell lines. Based on the study the compound BD1, BD3 and BD6 have emerged to be the most active compounds.

KEYWORDS

Molecular docking, Anti-oxidant, DPPH, Anti-cancer and Adriyamycin.

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INTRODUCTON

In synthetic medicinal chemistry, there are several privileged structures with different functional groups that can be considered for a variety of biological activities; 1, 5-benzothiazepines (BTZ), as part of one of such privileged scaffolds, has been of immense significance to the field of medicinal chemistry. Currently, BTZs are among the most broadly used drugs in the treatment of cardiovascular disorders, including examples such as Diltiazem, Thiazesim, and Clentiazem[1]. BTZ derivatives have been found to have activity against

different target proteins, andare of particular attention for lead development[2]. The BTZ nucleus has been used asa cardiovascular modulator acting on several G-protein coupled receptors as an antagonist[3], such as the anti-arrhythmic (CCK) receptor[4], Angiotensin-Converting Enzyme[5], Angiotensin II receptor[6], etc. Hemodynamic effects, anti-cancer activity[7] and spasmolytic activity[8-10], as well as anti-ulcer activity[11], have recently been reported, ashad a central nervous system depressant effect[12]. The inhibition of the tyrosine kinaseepidemic receptor of growth[13], which is related to the stabilization of the FKBP12 complex skeletal muscle channel–ryanodine receptor, has been reported. Phase II clinical trialson antiarrhythmic antihypertensive calcium (Ca^{2+}) channel antagonistic activity are being carried out on two spinoffs, one of which is 7-bromo-3(S)-butyl-3-ethyl-8-hydroxy-5-phenyl-2, 3, 4, 5-tetrahydro-1, 5-benzothiazepine-1, 1-dioxide (GW-577). Several BTZs are currently used in clinical practice; one of the most widely used classes is cardiovascular drugs such as diltiazem and clentiazem. As part of our ongoing efforts to identify new chemical entities (NCEs) endowed with biological activity, we considered the possibility of using a novel combination approach to the BTZ scaffold in order to investigate its anti-cancer properties. Numerous efforts have been undertaken in recent years for the development of new synthetic methodologies using renewable energy resources for shifting society away from non-renewable resources to environmentally-friendly biomass[14-18]. Organic molecules are key to this tedious process of drug discovery. In particular, there is a growing field of medicinal chemistry research that progresses heterocyclic materials; 1, 5-derivativeof BTZ, such as those previously discovered to be drug candidates, have always drawn special interest[19-21]. In the current investigation, we designed a novel BTZ scaffold containing compounds (Figure No.1) and employed an efficient approach for the synthesis of titled compounds.

MATERIAL AND METHODS

Material

All the solvents (AR grade) and reagents were dried and purified. The reactions were performed on oven dried glassware. All reagents and solvents were obtained from the supplier or recrystallized/redistilled unless otherwise noted. The purity of the synthesized compounds was monitored by thin layer chromatography (TLC). The reaction progress was monitored by TLC using precoated silica 60 F254, 0.25mm aluminum plates (Merck) and n-hexane: ethyl acetate (5:5) used as the mobile phase. The developed chromatogram was visualized by iodine vapor or UV chamber and melting points were determined in open capillary tubes. The melting points were recorded using Veego VMP-1 melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier Transform-Infrared Spectrometer using KBr pellets. Elemental analyses (C, H, and N) were done with a Shimadzu analyzer (Mumbai, Maharashtra, India) and all analyses were consistent (within 0.4%) with theoretical values. The ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds were recorded on a Bruker NMR Spectrometer (Billerica, MA, USA) at 400MHz frequency in deuterated DMSO and using TMS as an internal standard (chemical shift in ppm). The mass spectra of same compounds were scanned on Shimadzu ESI-MS.

EXPERIMENTAL SECTION

Step No.1: Synthesis of n- (2, 6- dimethylphenyl) acetamide (a)

A mixture of xylidine (0.01mol) in 40 ml DMF was added to the mixture of acetyl chloride (0.012mol) in triethylamine (0.012mol). Reaction mixtures were refluxed for 1h at 150-155□ until the starting material disappeared by TLC using ethyl acetate and n hexane (5:5) as mobile phase. After the reaction was completed, the precipitate formed upon cooling and it was filtered and recrystallized from ethanol to achieve the N-(2, 6-dimethylphenyl) acetamide (A).

Step No.2: Synthesis of substituted (z)-n-(2, 6-dimethylphenyl)-2-enamide (b1 to b6)

Various substituted aldehyde, N-(2, 6-dimethylphenyl) acetamide (A) and pyridine (1:1: 0.15mol.) were mixed in a flask, which boils at 105□, the heating was done on a water-bath for 8 hours: but this gave the unchanged aldehyde only. The heating was, therefore, done in an oil-bath at the usual temperature of 130-140□ ~ for 4 hours and when the contents were cold, methyl alcohol was added and the whole was left overnight. The product of Substituted (Z)-N-(2, 6-dimethylphenyl)-2-enamide was taken out as before by partial concentration of the filtrate and subsequent addition of acidulated water.

Step No.3: synthesis of n-(2, 6-dimethylphenyl)-2-substituted-2, 3-dihydrobenzo [b] [1, 4] thiazepin-3-amine

Various substituted N-(2, 6-dimethylphenyl)-2-enamide (0.1mmole) and *o*-aminothiophenol (0.1mmole) was dissolved in 20mL of ethanol. The reaction mixture was refluxed for 30 min for 65□. Completion of reaction was checked by TLC using ethyl acetate and n hexane (4:6) as mobile phase. After completion of the reaction the solid mass were separated out with high yield (90%).

Characterization of synthesised compounds (bd1 to bd6) N-(2, 6-dimethylphenyl)-2-methyl-2, 3 dihydrobenzo [b] [1, 4] thiazepin-3-amine (bd1)

$C_{18}H_{20}N_2S$; Colour: Pale yellow solid;% yield: 91%; MP: 171 – 173^oC; IR (KBr) cm^{-1}: 3357 (NH stretching, Amine); 3030 (CH stretching, Aromatic); 2732 (CH stretching, Alkane); 1407 (CN bending); 850 Aromatic ring; ^1H NMR (500 MHz, DMSO) δ 8.10 (s, 1H), 7.35 (d, J = 3.5 Hz, 2H), 7.21 (s, 1H), 7.14 (s, 1H), 6.99 – 6.83 (m, 2H), 6.60 (s, 1H), 5.24 (s, 1H), 3.30 (s, 1H), 3.09 (s, 1H), 2.25 – 2.21 (m, 6H), 1.40 – 1.26 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 170.31, 157.06, 155.82, 154.34, 134.70, 134.50, 129.99, 129.36, 129.30, 128.79, 128.02, 127.88, 127.26, 127.02, 126.63, 124.45, 123.71, 119.40, 119.01, 67.61, 64.87, 40.54, 20.89, 17.16. Mass: 296m/z; found 297 (M+1).

N-(2, 6-dimethylphenyl)-2-phenyl-2, 3-dihydrobenzo [b] [1, 4] thiazepin-3-amine (bd2)

$C_{23}H_{22}N_2S$; Colour: yellow solid; % yield: 86%; MP: 183 - 185^oC; 3357 (NH stretching, Amine); 3030 (CH stretching, Aromatic); 2732 (CH stretching, Alkane); 1407 (CN bending); 850 Aromatic ring; ^1H NMR (500 MHz, DMSO) δ 7.93 (s, 1H), 7.27 (t, J = 7.7 Hz, 3H), 7.22 – 7.14 (m, 5H), 7.09 (s, 1H), 6.97 – 6.82 (m, 2H), 6.57 (s, 1H), 5.87 (s, 1H), 4.81 (s, 1H), 3.98 (s, 1H), 2.21 - 2.17 (m, 6H); ^{13}C NMR (126 MHz, DMSO) δ 170.31, 157.06, 155.82, 154.34, 134.70, 134.50, 129.99, 129.36, 129.30, 128.79, 128.02, 127.88, 127.26, 127.02, 126.63, 124.45, 123.71, 119.40, 119.01, 108.40, 107.37, 67.61, 64.87, 18.37, 17.16. Mass: actual 353 m/z; found 352 (M-1).

N-(2, 6-dimethylphenyl)-2-(p-tolyl)-2, 3 dihydrobenzo [b] [1, 4] thiazepin-3-amine (bd3)

$C_{24}H_{24}N_2S$; Colour: yellow solid; % yield: 90%; MP: 183 - 185^oC; IR (KBr) cm^{-1}: 3357 (NH stretching, Amine); 3030 (CH stretching, Aromatic); 2732 (CH stretching, Alkane); 1407 (CN bending); 850 Aromatic ring; ^1H NMR (500 MHz, DMSO) δ 7.72 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 7.23 (s, 1H), 7.20 – 7.12 (m, 5H), 6.99 – 6.82 (m, 2H), 6.61 (s, 1H), 5.72 (s, 1H), 5.02 (s, 1H), 2.57 (s, 1H), 2.37 – 2.33 (m, 3H), 2.19 – 2.15 (m, 6H); ^{13}C NMR (126 MHz, DMSO) δ 168.50, 156.63, 148.92, 148.39, 125.64, 124.94, 123.24, 121.60, 109.19, 106.92, 106.34, 102.06, 20.90, 19.18, 17.77. Mass: actual 372 m/z; found 372 m/z.

N-(2, 6-dimethylphenyl)-2-(4-methoxyphenyl)-2, 3-dihydrobenzo [b] [1, 4] thiazepin-3-amine (bd4)

$C_{24}H_{24}N_2OS$; colour: Pale yellow; % yield: 89%; MP: 193 – 195^oC; IR (KBr) cm^{-1}: 3310 (NH stretching, Amine); 3030 (CH stretching, Aromatic); 2995 (CH stretching, Alkane); 1483 (CN bending); 85 (Aromatic ring); ^1H NMR (500 MHz, DMSO) δ 8.23 (s, 1H), 7.36 (s, 1H), 7.26 – 7.12 (m, 3H), 7.09 (d, J = 1.0 Hz, 2H), 6.98 – 6.88 (m, 2H), 6.87 – 6.78 (m, 2H), 6.60 (s, 1H), 5.88 (s, 1H), 4.99 (s, 1H), 3.82 – 3.78 (m, 3H), 2.84 (s, 1H), 2.17 – 2.13 (m, 6H).^{13}C NMR (126 MHz, DMSO) δ 168.50, 156.63, 137.77, 135.17, 128.98, 128.09, 126.06, 125.64, 124.94, 123.54, 123.24, 121.60,

65.51, 62.44, 19.18. Mass: actual 388 m/z; found 388 m/z.

4-(3-((2, 6-dimethylphenyl) amino)-2, 3-dihydrobenzo [b] [1, 4] thiazepin-2-yl) phenol (bd5)

$C_{23}H_{22}N_2OS$; Colour: yellow solid; % yield: 86%; MP: 172 – 175^oC; IR (KBr) cm^{-1}: 3310 (NH stretching, Amine); 2995 (CH stretching, Aromatic); 2600 (CH stretching, Alkane); 1483 (CN bending); 85 (Aromatic ring);^1H NMR (500 MHz, DMSO) δ 7.92 (s, 1H), 7.30 (s, 1H), 7.18 (d, J = 13.0 Hz, 2H), 7.09 (s, 2H), 7.02 – 6.94 (m, 1H), 6.94 – 6.82 (m, 2H), 6.82 – 6.68 (m, 2H), 6.57 (s, 1H), 5.87 (s, 1H), 4.72 (s, 1H), 4.04 (s, 1H), 3.63 (s, 1H), 2.21 – 2.17 (m, 6H); ^{13}C NMR (126 MHz, DMSO) δ 170.30, 155.81, 154.37, 134.50, 130.00, 129.31, 128.03, 127.26, 127.03, 124.45, 119.01, 108.40, 64.86, 56.41, 18.07. Mass: actual 374 m/z; found 374 m/z.

2-(4-chlorophenyl)-n-(2, 6-dimethylphenyl)-2, 3-dihydrobenzo [b] [1, 4] thiazepin-3-amine (bd6)

$C_{23}H_{21}ClN_2S$; colour: Pale yellow; % yield: 88%; MP: 175 – 178^oC; IR (KBr) cm^{-1}: 3357 (NH stretching, Amine); 3073 (CH stretching, Aromatic); 2985 (CH stretching, Alkane); 1407 (CN bending); 850 (Aromatic ring);^1H NMR (500 MHz, DMSO) δ 7.70 (s, 5H), 7.33 (dd, J = 21.6, 20.1 Hz, 19H), 7.27 (s, 1H), 7.24 (s, 5H), 7.22 – 7.12 (m, 15H), 7.00 – 6.83 (m, 10H), 6.61 (s, 5H), 5.61 (s, 5H), 4.33 (s, 5H), 2.60 (s, 5H), 2.24 – 2.20 (m, 29H). ^{13}C NMR (126 MHz, DMSO) δ 170.30, 155.98, 153.95, 135.46, 134.50, 131.51, 130.00, 129.31, 128.03, 127.26, 127.03, 124.45, 119.01, 108.17, 64.86, 56.41, 18.07. Mass: actual 392 m/z; found 395 (M+3).

***In-silico* molecular docking studies devices and materials**

In modern drug design, the docking is commonly used to understand the interaction between the target ligand-receptor and the target lead molecule's binding orientation with its protein receptor and is quite frequently used to detect the associations between the target components. The research work was done *in-silico* by utilizing bioinformatics tools. Also, we utilize some of the offline programming's like protein data bank (PDB) www.rcsb.org/pdb, PubChem database, Marvin sketch. The molecular docking studies were carried out through PyRx 0.9[22].

Preparation of protein

By utilizing the offline program protein data bank, we take the topoisomerase II (PDB ID: 1A35) with a resolution of 1.90A^o was obtained. From the protein we removed the crystal water, followed by the addition of missing hydrogens, protonation, ionization, energy minimization. The SPDBV (swiss protein data bank viewer) force field was applied for energy minimization. Prepared protein is validated by utilizing the Ramachandran plot[23].

Identification of active sites

Identification of active amino acid present in the protein is detected by using Protein-ligand interaction profile (PLIP) https://plip-tool.biotec.tu-dresden.de/plipweb/plip/index offline tool in google. From this, we found the active amino acid present in the protein[24].

Preparation of ligands

By utilizing the Marvin sketch tool, the molecules are designed in two and three-dimensional structures. After designed molecule, the structure was optimized in 3D optimization in Marvin sketch and saved as a pdb format[25].

DPPH radical assay

A total antioxidant capacity assay was carried out using DPPH as radical. The experimental procedure was adapted from the literature, only with slight modification. Briefly, 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical in ethanol (250mM, 2mL) was added to 2mL of an ethanolic solution of the test compounds. The final concentration of the test compounds in the reaction mixtures was 50mM. Each mixture was then shaken vigorously and held for 30 min at room temperature in the dark. The decrease in absorbance of DPPH at 517nm was then measured. DPPH solution (2mL) in ethanol (2mL) was used as blank and Ascorbic acid was used as control. All tests were performed in triplicate[26].

***In vitro* anticancer activity**

The *in vitro* cytotoxicity of the synthesized compounds was assessed against MCF-7 cancer cell line using SRB assay. The monolayer culture of the cell line was trypsinized, followed by adjusting the

cell count to 1.0 × 105 cells/mL by means of DMEM medium containing 10% FBS. The diluted cell suspension (0.1mL) was added to each well of the 96-well microtiter plate. The test wells were added with various concentrations (100µL) of test samples, and the control wells received media (100µL). The plates were then incubated at 37°C for 72 h in 5% CO2 atmosphere. After this duration, the cultures were fixed with trichloroacetic acid (25µL, 10% w/v) and stained for 30 min with sulforhodamine B (0.4% w/v) in acetic acid (1% v/v). Unbound dye was cleared by four washes with acetic acid (1% v/v), and protein-bound dye was extracted with 10mM unbuffered Trisbase [tris (hydroxymethyl) aminomethane]. The optical density of the protein-bound dye was recorded at 540nm[27]. The percentage cell viability (CV) was calculated using the following formula:

$$\text{Cell viability} = \frac{\text{Mean OD of individual test group}}{\text{Mean OD of control group}} \times 100$$

The concentration of test samples required to inhibit cell growth by 50% was tabulated from the dose-response for each cell line.

RESULTS AND DISCUSSION

Synthetic work

The compound N-(2, 6-dimethylphenyl) acetamide (A) was prepared by the reaction with A mixture of xylidine (0.01mol) in 40ml DMF was added to the mixture of acetyl chloride in triethylamine. Reaction mixtures were refluxed for 1h at 150-155^{o}C until the starting material disappeared by TLC using ethyl acetate and n hexane (5:5) as mobile phase. Further the compound A react with various substituted aldehyde, and pyridine at the temperature of 130-140^{o}C ~ for 4 hours, and when the contents were cold, methyl alcohol was added and the whole was left overnight. The product of Substituted (Z)-N-(2, 6-dimethylphenyl)-2-enamide (B1 - B6) was formed. Further the compound B1 - B6 was reacted with *o*-aminothiophenol and ethanol. The reaction mixture was refluxed for 30 min for 65^{o}C. Completion of reaction was checked by TLC using ethyl acetate and n hexane as mobile phase. After completion of the reaction the solid mass were separated out with high yield. The IR spectrum of the final synthesized compounds showed absorption bands around 3300-3200cm^{-1} for amine NH, while the distinguishing broad absorption peaks at 3030 were observed for CH aromatic, peaks at 1464-1400cm^{-1} for CN bending, and 800-700cm^{-1} for aromatic rings. These compounds also exhibited appropriate peaks at corresponding ppm in their ^{1}H NMR spectra. The ^{1}H NMR spectra of the synthesized compounds revealed a singlet signal at 8.7 for H of NH, doublet signal at 3-4 shows the CH_3 group and a signal at 7.5-6.5 for H of aromatic ring. The ^{13}C NMR spectra of synthesized compounds revealed a signal at 170 for carbonyl carbon, a signal at 155-160 for ethene carbon, signal at 20 for CH_3 group and a signal at 120-145 for aromatic carbon. The corresponding molecular ion peaks in the ESI–MS spectra were in conformity with the assigned structures. All the synthesized compounds were subjected to short-term *in-vitro* cytotoxicity studies using MCF-7 cell line and *in-vitro* anti-oxidant screening using DPPH scavenging method.

Molecular docking studies

Based on literature studies of BTZ derivatives, the 6 compounds were designed for our study and these 6 compounds were subjected to molecular docking studies. Molecular docking was carried out through PyRx 0.9 to predict the interactions model of the protein to its inhibitors. The molecular docking was performed to elucidate the binding mode competence of topoisomerase II and 6 BTZ analogues. The designed molecules were docked along with the reference standard, adriyamycin (ADR). The docking energy of our designed compounds ranged from 7.1to 7.9kcal/mol indicated good binding affinities to the target receptor, and the results are depicted in Table No.1. Among the docked compounds, derivative BD3and BD6 (-7.9kcal/mol) showed a significant binding energy towards the targeted enzyme. The compounds BD3possess2 hydrogen bonds between amino acids ASN 722 and MET428. The roles of certain crucial amino acids in the ligand-binding domain of the human topoisomerase II inhibitors were also established. Major non-covalent interactions

between the studied ligands and the ligand-binding domain of the topoisomerase II inhibitors were investigated. These amino acids have been repeatedly implicated during ligand interaction with the topoisomerase II inhibitors and also play important role in the inhibition of the ligand-binding domain of topoisomerase II inhibitors. These non-covalent interactions, van der Waals, columbic interaction, π–π interaction, and hydrogen interaction, are shown in Figure No.2 to Figure No.7.

Antioxidant Activity

The free radical scavenging activity of all compounds was carried out in the presence of the stable free radical (1, 1-diphenyl-2-picrylhydrazyl) DPPH using ascorbic acid antioxidant agents as positive control. Although a number of methods are available for determination of the antioxidant activity, the DPPH method is very common, rapid and has been shown to be one of the most appropriate methods. The inhibitory effects of different concentrations of synthesized compounds on DPPH radical are presented in Table No.2. The antioxidant activity is expressed in terms of % inhibition and IC_{50}.Based on the experimental results, among all the compounds synthesized compound BD1 substituted with acetaldehyde shows good inhibition (127.02µg/mL) compared to all the tested compounds.

***In- vitro* cytotoxic evaluation**

The targets compounds (BD1 – BD6) were evaluated for their anticancer activity against MCF – 7 cancer cell lines.

The IC_{50} values (concentration required to growth inhibition of 50%) for the synthesised compounds were determined using SRB assay. The cytotoxic evaluation results and IC_{50} values were listed in Table No.3 and well-known anticancer drug Adriamycin was used as positive control. The results indicated that all the tested compounds exhibited significant cell growth inhibition compared to reference standard against MCF – 7 cancer cell lines. The results were found that the synthesized compounds are relatively non-toxic at 100µg concentration in tested cell line. Among the tested compounds, compound BD3 substituted with methyl benzene group were found to have IC_{50} values 46.4023µg/mL against MCF – 7 cell lines cancer cell lines. Compound BD6 substituted with chloro-benzene were found to have IC_{50} values 95.8213µg/mL against MCF7 cancer cell lines. It was observed that most of the tested compounds demonstrated considerable anti-proliferative activity against tested cell lines. The compounds possessing halogen substitution and methyl substitution of the 2-phenyl ring on the benzothiazepine showed promising anticancer activities in the tested cell lines. The observed activity can be attributed to the activation of the ring by the electron-withdrawing nature of the halogen atoms. It was further observed in the docking studies of the compounds that BD3, BD6, and BD5 demonstrated favorable hydrophobic binding interactions with the proteins.

Table No.1: Docking results

S.No	Ligand	Binding Affinity (Kcal/mol)
1	BD1	-7.8
2	BD2	-7
3	BD3	-7.9
4	BD4	-7.2
5	BD5	-7.7
6	BD6	-7.9
7	ADR	-12.76

Table No.2: Anti-oxidant activity

S.No	Name of the compound	IC_{50}µg/Ml
1	BD1	127.02
2	BD2	313.37
3	BD3	265.83
4	BD4	189.84
5	BD5	264.98
6	BD6	150.97

Table No.3: *In vitro* cytotoxic evaluation of synthesised compounds against MCF – 7 cell line

S.No	Name of the compound	MCF 7 (IC_{50}µg/mL)
1	BD1	211.438
2	BD2	211.438
3	BD3	46.4023
4	BD4	136.539
5	BD5	106.644
6	BD6	95.8213
7	Adriyamycin	23.54

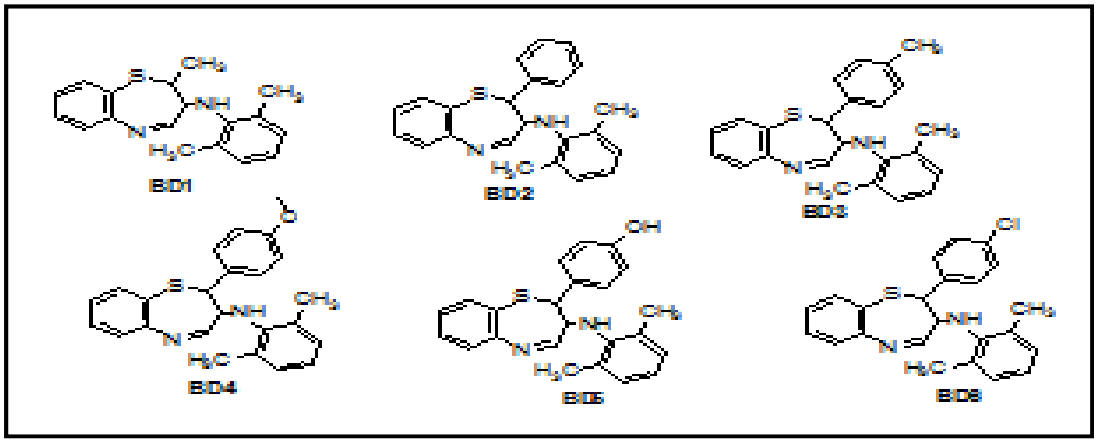

Figure No.1: Newly designed BTZ scaffold

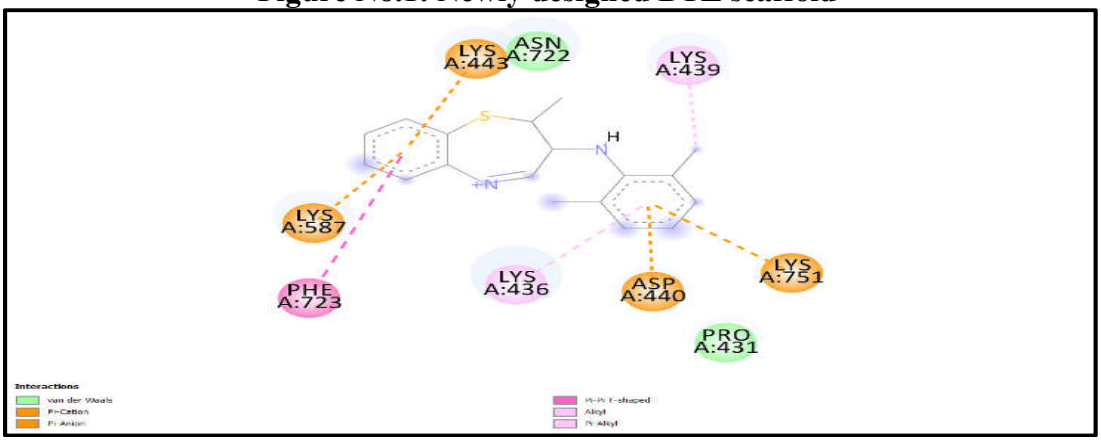

Figure No.2: Fitting pose with interactions of compound BD1 in the pocket of 1A35 in 2D view

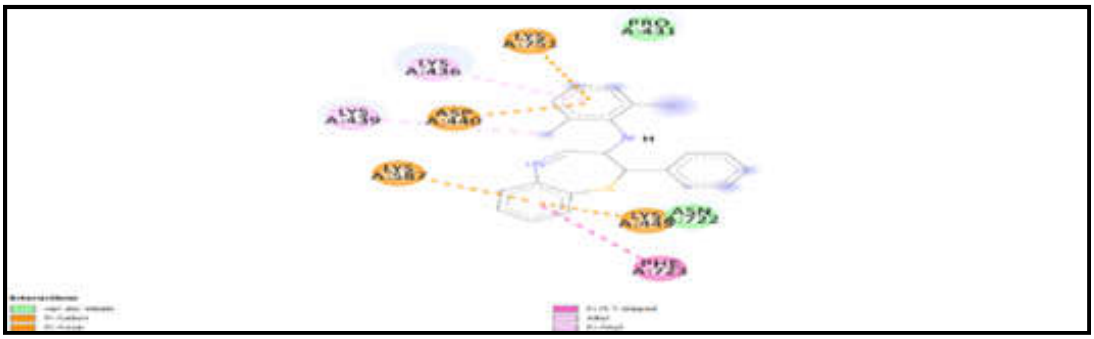

Figure No.3: Fitting pose with interactions of compound BD2 in the pocket of 1A35 in 2D view

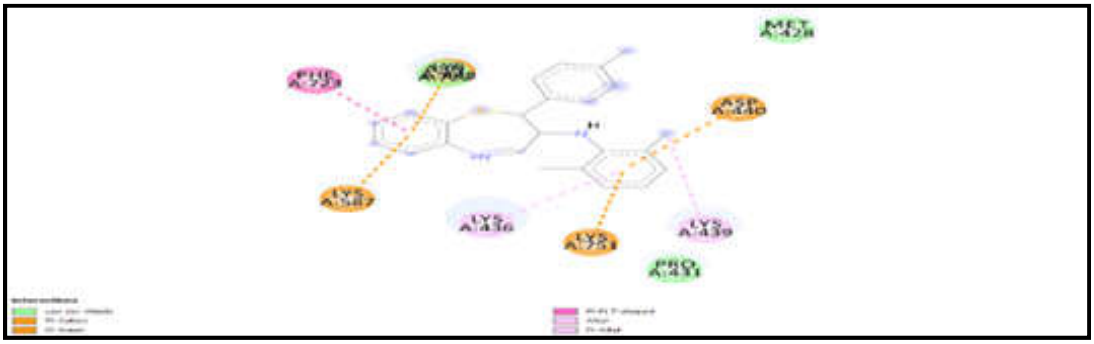

Figure No.4: Fitting pose with interactions of compound BD3 in the pocket of 1A35 in 2D view

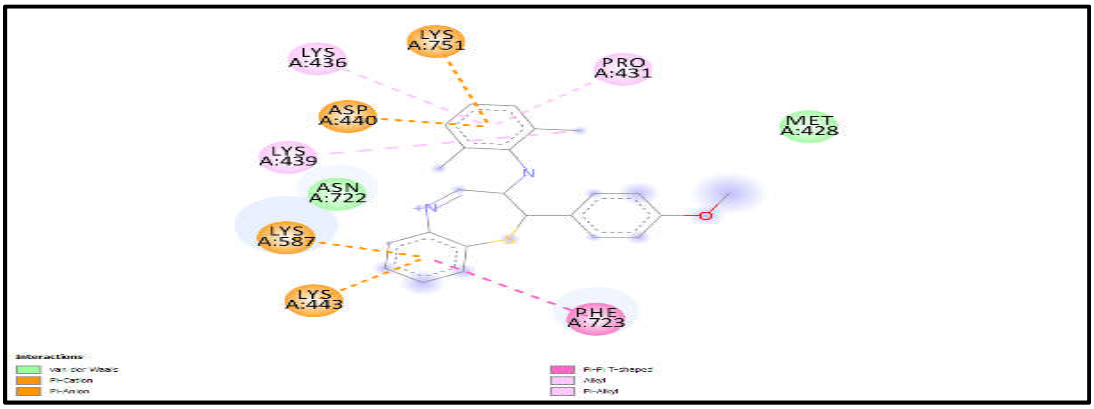

Figure No.5: Fitting pose with interactions of compound BD4 in the pocket of 1A35 in 2D view

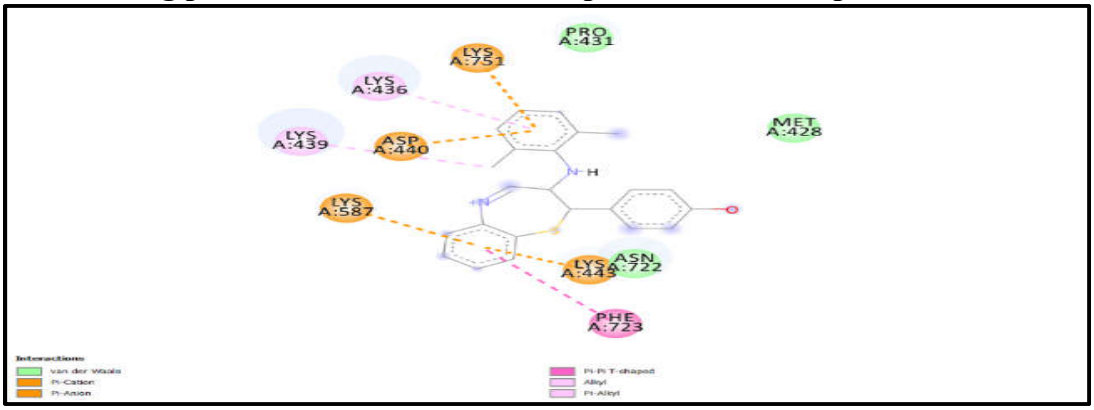

Figure No.6: Fitting pose with interactions of compound BD5 in the pocket of 1A35 in 2D view

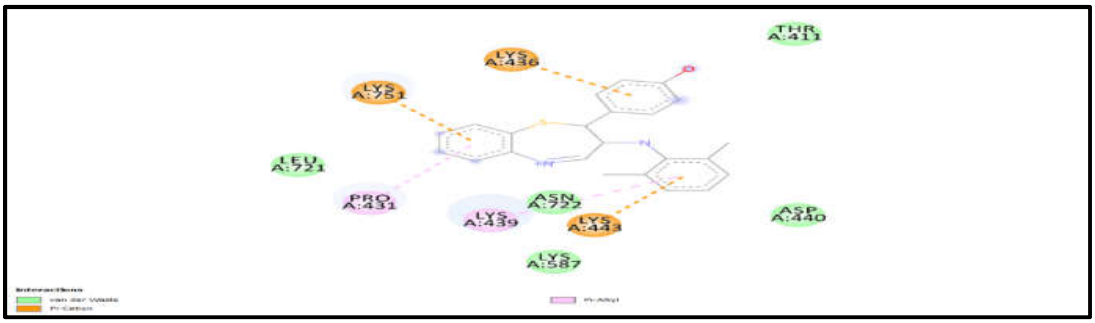

Figure No.7: Fitting pose with interactions of compound BD6 in the pocket of 1A35 in 2D view

CONCLUSION

The physicochemical and spectroscopic data confirmed the structural integrity of the newly synthesized compounds. The investigated molecules displayed a similar manner to protein binding to the active site of Topoisomerase II protein (PDB ID: 1A35) in molecular docking studies. The calculated docking energies indicated that its interaction with Topoisomerese II is favorable, but only to a limited extent. Based on the literature all the synthesised compounds are subjected to antioxidant activity by DPPH method. All the tested compounds exhibited maximum activity compared to the standard drug Ascorbic acid. Based on the study the compound BD1 and BD6 which is substituted with a electronegative groups like Chlorine and methyl produce a significant activity compared with standard drugs. All the synthesized compounds were screened for their *in vitro* viability test against MCF – 7, cancer cell lines. Compounds BD3 and BD6 emerged to be the most active compounds against tested cell lines. In addition, ADMET prediction results indicated that these compounds might possess less toxicity and pharmacokinetic properties. The study thus serves as an attempt to progress toward the discovery of novel drugs. Additional derivatives may be prepared and further extended in-depth investigations into *in-vivo* activity would be implemented to establish a SAR (Structural activity relationship) for rational study. From the present investigation, it may be concluded that the synthesised derivatives need to undergo further investigation to develop as a potential candidate drug.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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