

# Synthesis and Evaluation of Novel N-Cycloheptyl-Substituted -2,3- Dihydro-1,3-Benzothiazole-2-Carboxamide Targeting the Estrogen Binding Receptor

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## ABSTRACT

Bladder cancer is one of the deadly cancers with very limited options of treatment and lack of new drugs. Cisplatin, doxorubicin and thiotepa are the drugs mostly used in therapy. Nine new N-cycloheptyl-substituted- 2,3-dihydro-1,3-benzothiazole-2-carboxamide derivatives were designed using structure based drug discovery. The designed compounds were docked to ascertain their binding against bladder cancer cell lines (PDB code 3ERT). structure. The designed compounds were synthesised and characterized using different spectroscopic techniques. These novel compounds were evaluated on the MTT assay for their in vitro efficiency using the TCP1020 cell lines. The compounds 4e and 4i shown good inhibition. Two compounds of the series exhibit promising results which are in agreement with the in silico studies. The most potent compound against TCP1020 cell lines was compound 4i; IC<sub>50</sub> = 7.8 µM. The activity of the 4i will be due to the inhibition of estrogenic binding receptor.

**Keywords:** Bladder Cancer, Estrogenic Binding Receptor, Molecular Docking, Anticancer Activity.

## 1. INTRODUCTION

Urinary bladder cancer is one of the deadly cancers with 16,390 deaths in 2015-16 alone and 76,960 new cases. It is the ninth most widely occurring cancer throughout the world with male cases is high compared to females. The causes behind bladder cancer is mostly smoking, chemical contamination of drinking water, arsenic poisoning and schistosomiasis infection.<sup>1</sup> The matter of concern is more severe with very limited options of treatment and lack of new drugs, cisplatin, doxorubicin and thiotepa are drugs mostly used in therapy.<sup>2</sup> These all are very old drug and exhibits severe adverse reactions in patient with very less compatibility. This situation along with the epidemiological data calls for development of newer better and safer agents. Several attempts were reported for the development of newer agents for the treatment of bladder cancer like the peptides 9-mer bladder

cancer specific peptide (BP), Y-BP<sup>(3)</sup> and the 1-(N-methylindolyl)-3-phenylpropenones.<sup>(4)</sup> Tetracene derivatives have been traditionally used for the treatment of bladder cancer with the doxorubicin as most important drug of this series.<sup>(4-6)</sup>

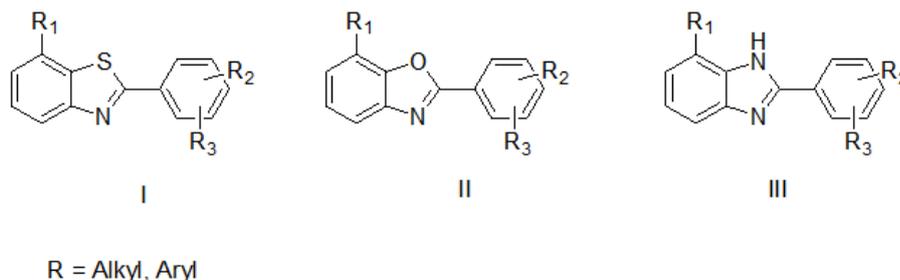
Similarly the benzothiazole derivatives (I-III) are reportedly found to be highly efficacious moiety for the development of newer candidates for the treatment of urinary bladder cancer and other types of cancers.<sup>(7,8)</sup> Recently the role of estrogen receptor in progression of bladder cancer was proved and it was also found that the inhibition of activity of this receptor or an control over its estrogen or progesterone binding region would help in prevention and cure of the urinary bladder cancer.<sup>(9,10)</sup> Based on these findings we initiated an attempt to develop lead molecules that would be helpful in controlling the progression and help cure the bladder cancer. Initially we designed sixteen novel benzothiazolyl derivatives (Scheme I) on the basis of earlier reported benzothiazoles as active moieties against the estrogenic binding receptors, then subjected them to molecular docking studies.<sup>11</sup> On the

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basis of molecular docking studies nine hybrid molecules containing benzothiazolyl and cycloheptyl moiety were synthesised and evaluated for their anticancer study on the

TCP1020 cell line.<sup>(12)</sup>

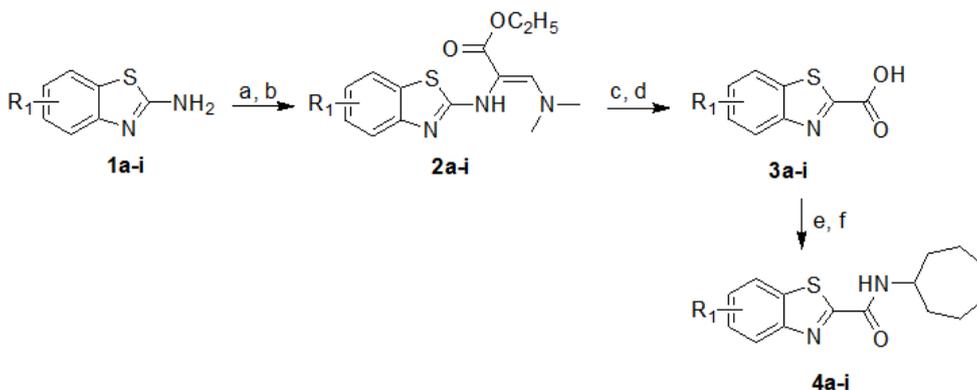


## 2. Material and Methods

Chemicals were obtained from Sigma Aldrich, USA. Melting points (Mp.) were detected with open capillaries using Thermo Precision Melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on FTIR-8400s spectrophotometer (Shimadzu, Japan). <sup>1</sup>H was obtained using a Bruker Advance-II 400 Spectrometer on 400 MHz using tetramethylsilane (TMS) as internal standard. All chemical shift values were recorded as  $\delta$

(ppm), coupling constant value  $J$  is measured in hertz, the peaks are presented as s (singlet), d (doublet), t (triplet), brs (broad singlet), dd (double doublet), m (multiplet). The purity of compounds was controlled by thin layer chromatography (Merck, silica gel, HF254–361, type 60, 0.25 mm, Darmstadt, Germany). Mass spectra (ESI-MS) were recorded at Waters, Q-TOF LC-MS spectrometer (Waters, Micromass LC-MS, USA).

### Synthesis:



Compound	4a	4b	4c	4d	4e	4f	4g	4h	4i
R <sub>1</sub>	4,6-dimethyl	4-CH <sub>3</sub>	5-CH <sub>3</sub>	6-CH <sub>3</sub>	7-CH <sub>3</sub>	5,7-dimethyl	6-Br	4,6-Dichloro	4,6-difluoro

Reagents and Conditions: a) Ethyl bromoacetate, K<sub>2</sub>CO<sub>3</sub>, acetone, 60 °C, overnight; (b) DMFDMA, 150 °C, 15h; (c) AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 24 h, rt; (d) LiOH, EtOH, reflux, 3 h; (e) EDC.HCl, HOBt, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12–16 h; (f) SnCl<sub>2</sub>, MeOH/EtOAc (4:1), H<sub>2</sub>.

Scheme I: Synthesis of various substituted *N*-cycloheptylbenzothiazole-2-carboxamides **4a-i**.

2.1 General procedure for synthesis of ethyl 2-(benzothiazol-2-ylamino)-3-(dimethylamino)acrylate (**2a-i**): (Scheme-I).

Various substituted 2-aminobenzothiazoles **1a-i** were reacted with ethyl bromoacetate in presence of potassium carbonate in acetone at 60 °C overnight. The recovered adduct was obtained as ethyl 2-[(substituted benzothiazolyl)amino]acetate which was reacted in turn with *N,N*-dimethylformamide dimethyl acetal at 150 °C for 15 h to yield the ethyl 2-(substituted benzothiazol-2-ylamino)-3-(dimethylamino)acrylates **2a-i**.

2.2. Synthesis of substituted benzothiazole-2-carboxylic acid (**3a-i**) (Scheme-I)

In next step, ethyl 2-(substituted benzothiazol-2-ylamino)-3-(dimethylamino)acrylates **2a-i** were treated with Lewis acid (AlCl<sub>3</sub>) leading to cyclization and yielding cyclized derivative as benzothiazolyl-2-carboxylates, which after basic hydrolysis gave the corresponding acids **3a-i**.

2.3. General procedure for synthesis of various substituted *N*-cycloheptylbenzothiazole-2-carboxamides **4a-i**. (Scheme-I).

The benzothiazolylcarboxylic acids **3a-i** were reacted with cycloheptylamine in presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride dissolved in butanol with dichloromethane as solvent for 12-16 h at room temperature. The adduct obtained was treated with tin chloride under hydrogen leading to final

derivatives as substituted *N*-cycloheptylbenzothiazole-2-carboxamides **4a-i**.

2.4. *In vitro* screening of compounds **4a-i**:

2.4.1. Cell culture

Human bladder cancer cell line TCP1020 was obtained from ATCC, USA. These were cultured in RPMI 1640 medium supplemented with 10% (v/v) fetal calf serum (FCS) and 2 mM glutamine (Sigma, USA). Cells were maintained at 37 °C in a 5% CO<sub>2</sub>-humidified chamber to ensure freedom from unwanted bacteria.

2.4.2. Cell proliferation assay

Efficacy of the newly synthesised compounds was measured by a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay by method described earlier.<sup>11</sup> TCP1020 cells were seeded into 96-well plates (3 x 10<sup>3</sup> cells/well) in 100 µl of culture medium. After 24 h, cells were treated with doxorubicin (Sigma-Aldrich, USA) and the cycloheptylbenzothiazole-2-carboxamides at various concentrations. In parallel, a control with DMSO in concentration was employed as vehicle. The incubation was carried out for 48 h after that 10 µL of a MTT stock solution in PBS at 5 mg/mL was added in each well. These plates were again incubated at 37 °C for 3 h. These plates were then subjected to centrifugation for 5 min at 1500 rpm. The supernatant medium was discarded and replaced with fresh DMSO to solubilize purple formazan crystals. Following to this the mixture was shaken for 15 min and then the absorbance was measured on an ELISA reader at 570 nm with reference wavelength of 650 nm. Absorbance observed from control was treated as 100% of cell survival; reading was taken in triplicate for each data point.

2.5. Molecular docking study

The compounds library 4a-i was constructed using the fragment dictionary of Maestro 7.5 and geometry

optimized by Macromodel program v9.1 (Schrodinger, LLC) using the Optimized Potentials for Liquid Simulations-all atom (OPLS-2005) force field with the steepest descent followed by truncated Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-2005 force field.

The docking calculations were performed using the "Extra Precision" (XP) mode of Glide module (Schrodinger software) and the 2005 implementation of the OPLS-2005 force field. The details about the protocols of Glide are described elsewhere<sup>(13-16)</sup>, a short description is provided below. Various energy grids for binding sites were calculated and stored and is defined in terms of two concentric cubes: the bounding box, which contains the center of any acceptable ligand pose, and the enclosing box, which contains all ligand atoms of an acceptable pose. Cubes with an edge length of 10 Å and centered at the midpoint of the longest atom-atom distance in the respective crystallized ligand demarcated the bounding box in the protein. Poses with an RMSD of less than 0.5 Å and a maximum atomic displacement of less than 1.3 Å were excluded as redundant in order to increase diversity in the retained ligand poses. The scale factor for van der Waals radii was applied to the atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of conjugate gradient. Upon completion of each docking calculation, at most 100 poses per ligand were generated. The best docked structure was chosen using a Glidescore (Gscore) function. The Gscore is a modified and extended version of the empirically based Chemscore function.<sup>17</sup> Another scoring function used by Glide is Emodel, which itself derived from a combination of the Gscore, Coulombic, van der Waals and the strain energy of the ligand. All computations were carried out on a Dell Precision 470n dual processor with the Linux OS (Red Hat Enterprise WS 4.0).<sup>(18-20)</sup>

### 3. Results and Discussion

#### 3.1. Synthesis:

##### 3.1.1. Synthesis of N-cycloheptyl -5,7-dimethylbenzo [d]thiazole-2-carboxamide **4a**.

Mp: 231-234 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.22-1.62 (m, 12H, cycloheptyl ring), 2.32 (s, 6H, CH<sub>3</sub>), 3.58 (m, 1H, methylene), 6.86 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); Anal.Calcd for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>OS: C, 67.51; H, 7.33; N, 9.26; O, 5.29; S, 10.60.

##### 3.1.2. Synthesis of N-cycloheptyl-7-methylbenzo [d] thiazole-2-carboxamide **4b**.

Mp: 237-239 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.29-1.63 (m, 12H, cycloheptyl ring), 2.36 (s, 6H, CH<sub>3</sub>), 3.58 (m, 1H, methylene), 6.84 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); MS (ESI) m/z: 288.1296; Anal.Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>OS: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12

##### 3.1.3. Synthesis of N-cycloheptyl-6-methylbenzo [d] thiazole-2-carboxamide **4c**

Mp: 232-234 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.67 (m, 12H, cycloheptyl ring), 2.32 (s, 6H, CH<sub>3</sub>), 3.57 (m, 1H, methylene), 6.84 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); MS (ESI) m/z: 288.1296; Anal.Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>OS: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12

##### 3.1.4. Synthesis of N-cycloheptyl-5-methylbenzo [d] thiazole-2-carboxamide **4d**.

Mp: 233-235 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.61 (m, 12H, cycloheptyl ring), 2.33 (s, 6H, CH<sub>3</sub>), 3.55 (m, 1H, methylene), 6.86 (m, 1H, benzothiazole), 7.72 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); MS (ESI) m/z: 288.1296; Anal.Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>OS: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12.

##### 3.1.5. Synthesis of N-cycloheptyl-4-methylbenzo [d] thiazole-2-carboxamide **4e**.

Mp: 234-236 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.65 (m, 12H, cycloheptyl ring), 2.34 (s, 6H, CH<sub>3</sub>), 3.53 (m, 1H, methylene), 6.81 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); Anal.Calcd for

C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>OS: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12

3.1.6. Synthesis of N-cycloheptyl-4,6-dimethylbenzo [d] thiazole-2-carboxamide **4f**.

Mp: 244-246 C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.22-1.63 (m, 12H, cycloheptyl ring), 2.31 (s, 6H, CH<sub>3</sub>), 3.50 (m, 1H, methylene), 6.81 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.4 (s, 1H, NH); Anal. Calcd for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>OS: C, 67.51; H, 7.33; N, 9.26; O, 5.29; S, 10.60

3.1.7. Synthesis of 5-bromo-N-cycloheptylbenzo [d] thiazole-2-carboxamide **4g**.

Mp: 212-214 C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.69 (m, 12H, cycloheptyl ring), 3.60 (m, 1H, methylene), 6.80 (m, 2H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); MS (ESI) m/z: 302.1453; MS (ESI) m/z: 352.0245; Anal. Calcd for C<sub>15</sub>H<sub>17</sub>BrN<sub>2</sub>OS: C, 51.00; H, 4.85; Br, 22.62; N, 7.93; O, 4.53; S, 9.08.

3.1.8. Synthesis of 5,7-dichloro-N-cycloheptylbenzo [d] thiazole-2-carboxamide **4h**

Mp: 219-221 C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.63 (m, 12H, cycloheptyl ring), 3.58 (m, 1H, methylene), 6.97 (m, 1H, benzothiazole), 7.71 (m, 1H, benzothiazole), 8.1 (s, 1H, NH); MS (ESI) m/z: 302.1453; MS (ESI) m/z: 342.0360; Anal. Calcd for C<sub>15</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>OS: C, 52.48; H, 4.70; Cl, 20.66; N, 8.16; O, 4.66; S, 9.34.

3.1.9. Synthesis of N-cycloheptyl-5,7-difluorobenzo [d] thiazole-2-carboxamide **4i**.

Mp: 119-121 C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.27-1.53 (m, 12H, cycloheptyl ring), 3.54 (m, 1H, methylene), 6.97 (m, 1H, benzothiazole), 7.79 (m, 1H, benzothiazole), 8.9 (s, 1H, NH); MS (ESI) m/z: 302.1453; MS (ESI) m/z: 310.0951; Anal. Calcd for C<sub>15</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>OS: C, 58.05; H, 5.20; F, 12.24; N, 9.03; O, 5.16; S, 10.33.

The present investigation addresses the importance and lack of drugs for the treatment of bladder cancer. Herein, we have reported the design and synthesis of novel benzothiazolyl derivatives that show good *in vitro* activity against the bladder cancer cell lines. On the basis of literature we designed sixteen benzothiazolyl derivatives; these compounds were subjected to molecular docking

studies. The molecular docking was carried out on the estrogen binding receptor. To perform the molecular docking studies we retrieved the crystal structure of estrogen binding receptor from the protein data bank (PDB: 3ERT). It is reported that in most cases of bladder cancer the estrogen binding receptor plays major role in carcinogenesis, if this receptor is regulated then normal apoptosis will be resumed. The molecular docking experiment was carried out with all the sixteen molecules, but it was found that only nine molecules of the series provided with significant score and hence these are only presented in the study (Figure 1, Table 1). The compound 4i shown the hydrogen bonding with THR347 residue with bond distance 2.01 Å and compound 4e shown the hydrogen bonding with LEU346 residue with bond distance 2.36°. Surprisingly it was found that the binding to the receptor of the same series is through the different H-bonding network. While the benzothiazole and Compounds with methyl and halogen substituted on the benzothiazole nucleus displayed good docking score in the range of -6.12 to -3.24 with compound 4i exhibiting highest score and 4g with lowest.

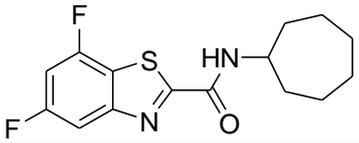
Accordingly, nine compounds were synthesised following appropriate route, in the first step various substituted 2-amino benzothiazolyl 1a-i derivatives were obtained and treated with ethyl bromoacetate and DMFDMA to yield the corresponding acrylate 2a-i. These compounds under the influence of aluminium trichloride and lithium hydroxide yield the substituted benzothiazolyl acids 3a-i. These were reacted with cycloheptyl amides in presence of EDC.HCl and further reduced by tin chloride to yield the final derivatives as substituted N-cycloheptylbenzothiazole-2-carboxamides 4a-i, these compounds were structurally elucidated with help of mass analysis and proton NMR. The proton NMR exhibited prominent peaks pertaining to the cycloheptyl moiety in the upfield region with protons around δ 1.22-1.62 ppm with a multiplet. The methyne proton was observed around δ 3.58 ppm and the amide proton was found at δ 8.1 ppm which is characteristic feature of these compounds. The

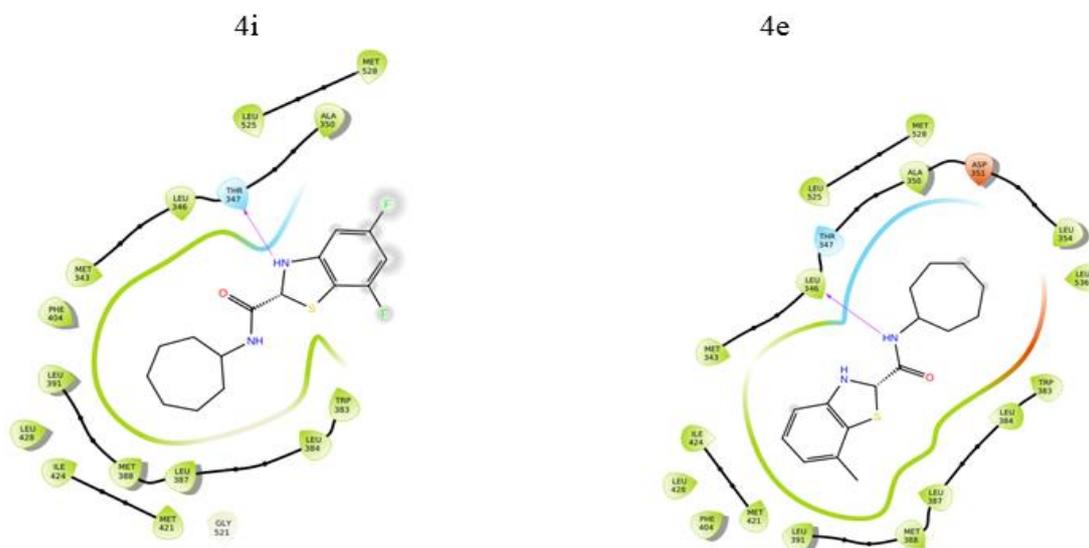
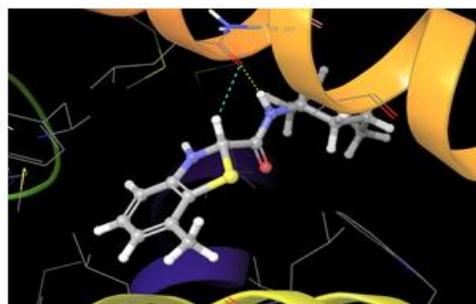
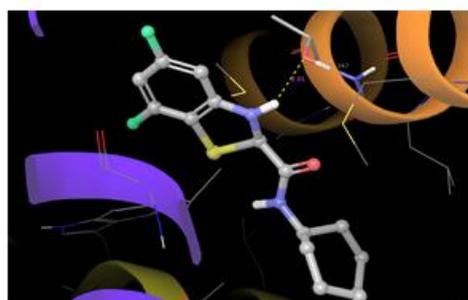
mass analysis and elemental analysis confirmed the final derivatives.

**Table (1)**

**Antiproliferative profile of the novel *N*-cycloheptylbenzothiazole-2-carboxamides derivatives. The table represents conc. as a result of 50% loss of cell viability with respect to untreated cells (IC<sub>50</sub>), the results were resolute from dose-response curves. Values are presented as means ± SD of three independent experiments**

Compd. no.	Structure	IUPAC name	IC <sub>50</sub> (μM)	Dock score
4a		N-cycloheptyl-5,7-dimethylbenzo[d]thiazole-2-carboxamide	14.7 ± 0.6	-5.01
4b		N-cycloheptyl-7-methylbenzo[d]thiazole-2-carboxamide	14.4 ± 0.5	-5.13
4c		N-cycloheptyl-6-methylbenzo[d]thiazole-2-carboxamide	13.4 ± 0.4	-5.72
4d		N-cycloheptyl-5-methylbenzo[d]thiazole-2-carboxamide	14.5 ± 0.5	-4.99
4e		N-cycloheptyl-4-methylbenzo[d]thiazole-2-carboxamide	10.1 ± 0.2	-5.78
4f		N-cycloheptyl-4,6-dimethylbenzo[d]thiazole-2-carboxamide	14.6 ± 0.4	-5.74
4g		5-bromo-N-cycloheptylbenzo[d]thiazole-2-carboxamide	17.2 ± 0.2	-3.24
4h		5,7-dichloro-N-cycloheptylbenzo[d]thiazole-2-carboxamide	15.2 ± 0.3	-5.60

Compd. no.	Structure	IUPAC name	IC <sub>50</sub> (μM)	Dock score
4i		N-cycloheptyl-5,7-difluorobenzo[d]thiazole-2-carboxamide	7.8 ± 0.7	-6.12
Std	Doxorubicin	--	6.7 ± 0.5	-6.33



**Figure (1): XPLGlide-predicted pose for representative compounds 4i and 4e with the estrogenic binding receptor active site. For clarity, only the polar hydrogen is shown. Hydrogen bonds are shown as dotted yellow lines. While the inhibitor is shown as ball and stick model**

These compounds were subjected to the anticancer activity following standard MTT assay protocol using

TCP1020 cell line obtained from the ATCC. The compound doxorubicin was used as standard drug, as this was also used in the molecular docking study. The experimental part is well established and was followed according to the earlier reported methods. The results were derived after three independent experiments were repeated and the IC<sub>50</sub> was calculated for each of the molecule including standard drug (Table 1). It was found that the standard drug presents IC<sub>50</sub> of 6.7. In comparison to the experimental compounds the compound 4i has IC<sub>50</sub> of 7.8 which is highest in the series followed by 4e with IC<sub>50</sub> of 10 (Table 1). These results are quit significant as these values correspond to our findings from the molecular docking studies. It was found that the compounds with methyl group adjacent to the nitrogen of the benzothiazolyl nucleus have good activity whereas, the molecules with halogens also displayed greater activity, and the fluoro substituted molecule displayed the highest activity. It can be derived that the presence of methyl group and halogen

on the phenyl ring of the benzothiazolyl moiety would help increase in activity.

#### 4. Conclusion

The present investigation exhibits the benefits of designing and developing new heterocyclic compounds for their anticancer activity. These compounds were successfully designed, synthesised and evaluated nine novel derivatives of benzothiazole and cyclic heptylamines. These compounds were found to be highly active on the bladder cancer cell lines, moreover, compound 4a-i was found to be more active comparable to doxorubicin. These compounds can be further improved for their activity and could serve as lead molecules for the bladder cancer.

#### 5. Conflict of Interest

None to Declare.

## REFERENCES

- (1) <http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/bladder-cancer-statistics>, retrieved on 17th April, 2016.
- (2) Dayssy A. Diaz, Alan Pollack, Matthew C. Abramowitz, and Bladder Cancer: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy, ed Nancy Y. Lee • Jiade J. Lu, Springer Verlag, GmBH, Germany, DOI: 10.1007/978-3-642-28860-9.
- (3) Su Ha Y, Lee H, An G, Kim J, Kwak W, Lee E, Yoo J. Synthesis and evaluation of a radioiodinated bladder cancer specific peptide. *Bioorganic & Medicinal Chemistry*. 2012; 20: 4330-4335.
- (4) Martel-Frchet V, Kadri M, Ronot X, Structural requirement of arylindolylpropenones as anti-bladder carcinoma cells agents, *Bioorganic & Medicinal Chemistry*, 2011; 19: 6143-6148.
- (5) Liang J, Yang V, Synthesis of doxorubicin-peptide conjugate with multidrug resistant tumor cell killing activity. *Bioorganic & Medicinal Chemistry Letters*. 2005; 15: 5071-5075.
- (6) Burke P, Koch T. Design, Synthesis, and Biological Evaluation of Doxorubicin-Formaldehyde Conjugates Targeted to Breast Cancer Cells. *J. Med. Chem.* 2004; 47:1193-1206.
- (7) Benzoxazole, benzothiazole, and benzimidazole derivatives for the treatment of cancer and other diseases, US 20050014767 A1.
- (8) Benzothiazole derivatives and a use thereof for the treatment of cancer, US 20160016943 A1.
- (9) Shen S, Smith C, Hsieh J. Expression of estrogen receptors- $\alpha$  and - $\beta$  in bladder cancer cell lines and human bladder tumor tissue. *Cancer*. 2006; 106:2610-2616.
- (10) Mashhadi R, Pourmand G, Kosari F, Alizadeh F. Role of Steroid Hormone Receptors in Formation and

- Progression of Bladder Carcinoma: A Case-Control Study. *Urological Oncology*. 2014; 11: 1969.
- (11) Chikhale R, Thorat S, Pant A, Jadhav A, Thatipamula K, Bansode R, Khedekar P. Design, synthesis and pharmacological evaluation of pyrimidobenzothiazole-3-carboxylate derivatives as selective L-type calcium channel blockers. *Bioorg. Med. Chem.* 2015; 23: 6689-6714.
- (12) Liang J, Yang V. Synthesis of doxorubicin-peptide conjugate with multidrug resistant tumor cell killing activity. *Bioorganic & Medicinal Chemistry Letters* 2005; 15: 5071-5075.
- (13) Bytheway, I. Cochran, S. Validation of Molecular Docking Calculations Involving FGF-1 and FGF-2, *J. Med. Chem.* 47 (2004) 1683.
- (14) Chen, H. Lyne, P.D. Giordanetto, F Lovell, T. Li, J. On Evaluating Molecular-Docking Methods for Pose Prediction and Enrichment Factors *Chem. Inf. Model.* 46 (2006) 401.
- (15) . Friesner, R.A. et al. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy, *J. Med. Chem.* 47 (2004) 1739.
- (16) . Halgren, T.A. Murphy, R.B. Friesner, R.A Beard, H.S. . Frye, L.L. Pollard W.T.
- (17) Banks, J.L. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening, *J. Med. Chem.* 47 (2004) 1750.
- (18) . Eldridge, M.D Murray, C.W. . Auton, T.R Paolini, G.V. Mee, R.P. Molecular modeling of fentanyl analogs, *J. Comput. -Aided Mol. Des.* 11 (1997) 425.
- (19) Anand, P. and Singh B., Synthesis and evaluation of novel 4-[(3H, 3aH, 6aH) -3-phenyl) -4,6-dioxo-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazol-5(3H, 6H, 6aH)- yl] benzoic acid derivatives as potent acetylcholinesterase inhibitors and anti-amnestic agents. *Bioorganic & Medicinal Chemistry*, 2012. 20 (1): p. 521-530.
- (20) Temperini, A. et al., Additive-free chemoselective acylation of amines. *Synthetic Communications*, 2010; 40 (2): 295-302.
- (21) van Horsen, W.B., Nitration of benzanilide and its derivatives. *Recl. Trav. Chim. Pays-Bas Belg.*, 1936; 55: 245-62.

## تصنيع وتقييم مركبات جديدة تستهدف رابط مستقبل الأستروجين (Novel N-Cycloheptyl-Substituted -2,3- Dihydro-1,3- Benzothiazole-2- Carboxamide)

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### ملخص

يتميز سرطان الثدي من أكثر أنواع السرطانات المميتة وفرص محدودة للعلاج وعدم توفر أدوية جديدة لمعالجته. تعتبر الأدوية سسبلاتين، دوكسوروبيسين وثيوتيبيا الأكثر استخداماً في العلاج. تسعة مركبات مشتقة كيميائياً تم تعميمها بناءً على اكتشاف الأدوية بناءً على التركيبة الكيميائية، هذه المركبات ترتبط كيميائياً ضد خطوط خلايا السرطان بالثلاثة.

هذه المركبات تم تخليقها باستخدام آليات التحليل الطيفي المختلفة، ثم تم تقييمها على طريقة MTT لاختبار فعاليتها بالمختبر، تبين أن مركبين اثنين (4e و 4i) أظهرتا تثبيط جيد مما يتناسب مع نتائج دراسات أخرى، وتبين أن المركب الأكثر فعالية هو (4i)، والعائدة للارتباط بالمستقبل الاستروجيني وتثبيطه.

**الكلمات الدالة:** سرطان الثدي، المستقبل الاستروجيني المرتبط، ارتباط جزيئي، نشاط ضد السرطان.