In-silico Molecular Docking and ADME/Pharmacokinetic Prediction Studies of Some Novel Benzothiazole Derivatives as Anticancer Agents for the Treatment of Breast Cancer

Khyati N. Bhagdev[1*], Chintankumar J. Tank[2]

[1]*Research Scholar, School of Pharmacy, Dr. Subhash University, Junagadh, India
[2]Professor, School of Pharmacy, Dr. Subhash University, Junagadh, India
*Address of the correspondance
Khyati Bhagdev
Research Scholar
School of Pharmacy
Dr. Subhash University,
Dr. Subhash road,
Junagadh, 362001
Gujarat
India
Tel: + 91 7600023301,
email: khyatiiibhupta@gmail.com

Abstract

Molecular docking simulation of 3 molecules of N-(1H-benzo[d]imidazol-2-yl)-7-chloro-6-fluorobenzo[d]thiazol-2-amine with the target receptor aromatase was carried out so as to evaluate their theoretical binding affinities. The chemical structure of the molecules was accurately drawn using ChemDraw Ultra software, then optimized at density functional theory (DFT) using Becke's three-parameter Lee–Yang–Parr hybrid functional (B3LYP/6-311**) basis set in a vacuum of Spartan 14 software. Subsequently, the docking operation was carried out using PyRx virtual screening software. Three compounds were developed by fusion of a benzothiazole and benzimidazole ring system targeting the treatment of breast cancer. The marketed drug Exemestane which is also an aromatase inhibitor was used as a reference molecule for docking. The highest docking score from all three molecules was -8.6 kcal/mol which is very near to the standard drug score -9.5 kcal/mol which suggests that the compound exhibited favorable protein–ligand interactions, indicating its potential as a lead candidate for further investigation. In-silico ADME and drug-likeness prediction of the molecules showed good pharmacokinetic properties having high gastrointestinal absorption, orally bioavailable, and less toxic. The outcome of the present research strengthens the relevance of these compounds as promising lead candidates for the treatment of breast cancer which could help the medicinal chemists and pharmaceutical professionals in further designing and synthesis of more potent drug candidates. Moreover, the research also encouraged the in vivo and in vitro evaluation study for the proposed designed compounds to validate the computational findings.

Keywords: Molecular docking · Binding affinity · Active sites · Pharmacokinetics · Molecular interactions · Hydrogen bond

How to cite this article: Bhagdev KN, Tank CJ. In silico Molecular Docking and ADME/Pharmacokinetic Prediction Studies of Some Novel Benzothiazole Derivatives as Anticancer Agents for the treatment of breast cancer. Int J Drug Deliv Technol. 2026;16(62s): 1825-1829. DOI: 10.25258/ijddt.16.62s.184

Source of support: Nil.

Conflict of interest: None.

1. Introduction

Breast cancer is among the most prevalent cancers and is the leading cause of cancer death in women worldwide. It is a heterogeneous disease, characterized by uncontrolled growth of breast epithelial cells[1]. Hormone receptor-positive breast cancer is a subtype of breast cancer that accounts for about 70% of all breast cancer cases and is highly estrogen-dependent for tumour growth and progression[2,3].

Aromatase, a cytochrome P450 enzyme encoded by CYP19A1 gene, is a key enzyme in the biosynthesis of estrogens, catalyzing the conversion of androgens to estrogens[4]. In postmenopausal women, aromatase activity in peripheral tissues is the main source of estrogen production. High serum estrogen levels promote proliferation of estrogen receptor-positive (ER+) breast cancer cells, contributing to disease development and progression[5].

Aromatase inhibition has become a successful therapeutic approach in the treatment of hormone-dependent breast cancer[6]. Aromatase inhibitors (AIs) such as Anastrozole, Letrozole and Exemestane reduce the production of estrogen and

suppress estrogen-mediated tumor growth. These agents have shown significant clinical benefits and are now widely used as first-line therapy in postmenopausal women with ER-positive breast cancer[7]. Exemestane was used as a standard drug here.

Though the existing aromatase inhibitors are effective, issues like side effects, drug resistance, and relapse demand the need for the new therapeutic agents. Traditional methods for synthesizing new drug compounds is costly and time-consuming. Molecular docking is one of the CADD techniques that predicts the binding affinity as well as the best binding pose of the molecule with the active site of a target (receptor), and it is crucial when carrying out a structure-based drug design (SBDD)[8]. Virtual docking rationalizes screening new lead compounds and also provides a hint on structure–activity relationships (SARs) and mode(s) of activity action based on scoring function and further binding modes analysis from ligand–protein binding/interaction studies[9].

In silico physicochemical properties of a molecule such as saturation, lipophilicity, polarity, size, solubility, and flexibility give vital information on whether the molecule can serve as a drug at an early stage of development. Computational methods such as molecular docking and in silico drug design provide useful tools for identifying and optimizing novel aromatase inhibitors with enhanced efficacy and safety profiles[10]. Hence, the present study aims at the design and molecular docking analysis of novel compounds against aromatase as potential therapeutic candidates for the treatment of breast cancer. Also, in silico absorption, distribution, metabolism, and excretion (ADME) and drug likeness properties of molecules were analysed.

2. Methodology

2.1 Computer System and Software

Computer system (Dell), with the following specification properties; CPU Dual@0.30 GHz, Intel® Core i3-6100U, 12 Gigabyte RAM was used throughout the present study. The software download and installed include PyRx virtual screening software, Spartan'14V 1.1.4, Discovery Studio Visualizer v16.1.0.15350, Chemdraw Ultra software V. 12.0.2, Spartan'14V 1.1.4 developed by Wave function Inc., Swiss ADME online software.

2.2 In-Silico Docking And ADME/Pharmacokinetics Prediction

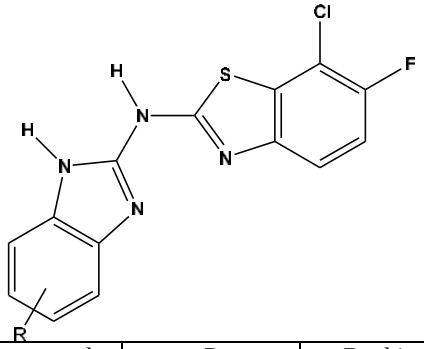
Three novel synthesized benzothiazole molecules were taken as anti-cancer agents[11]. The chemical structure of the molecules was accurately drawn with ChemDraw Ultra level software V12.0.2 (Table 1), then optimized with Spartan 14 software at density functional theory (DFT) with Becke's three-parameter Lee–Yang–Parr hybrid functional (B3LYP/6-31G** basis set) in a vacuum[12], which was later saved as Protein Data Bank (PDB) file format. In principle, the geometry optimization using the DFT level of theory as aniterative process for the search of the lowest energy conformer give the most stable conformation of each molecule in the dataset[13]. The aromatase structure (PDB ID: 3s7s) was downloaded as the receptor from the PDB website: https ://www.rcsb.org . In-silico docking operation was carried out on the 3 molecules with the downloaded receptor using AutoDock Vina of PyRx virtual screening software[14]. The vina wizard uses a stochastic gradient optimization algorithm for predicting the binding affinities between ligands and receptors. The docking output with the highest binding affinity was visualized to study the residual interactions using Discovery Studio Visualizer. Figure 2 shows the 3D prepared aromatase target with all 3 ligands. Furthermore, the Simplified Molecular Input Line Entry System (SMILES) format of the molecules was pasted on the swissADME webserver (Swiss Institute of Bioinfor matics, Switzerland) to generate their ADME/pharmacokinetic profile and drug-likeness parameters and PROTOX III was used to check the toxicity of all three compounds.

3. Results and Discussion

3.1 Molecular Docking and Virtual Screening

Molecular docking is a simulation technique that explores ligand's best binding pose with the active site of a target. This technique involves the selection of 3D- coordinate space of the binding site in the target and calculating the binding affinity of the resultant orientation of the molecule within the binding site which forms the complex[15]. The significance and sensitivity of binding affinity values are determined by the largest magnitude negative number (highest binding affinity or lowest binding energy) depicting the most favourable conformation of the complex formed when the ligand involved efficiently binds with the active pockets of the target. In addition, the molecular docking simulation was performed to validate the anti-cancer efficacy of synthesized benzothiazole derivatives by investigating binding modes as well as orientation of ligands in the receptor pocket of aromatase target. The docking poses were ranked according to their score values, and Table 1 showed binding affinities of the best pose of the selected 3 synthesized molecules with the aromatase target. It was observed that the binding affinity of complexes ranged from – 8.1 to – 8.6 kcal/mol which confirmed their excellent potency. All the three molecules a, b and c with their binding affinity with aromatase receptor were reported to have good binding affinity with the receptor.

Table 1. Molecular binding affinities of benzothiazole derivatives with Aromatase receptor (PDB ID: 3S7S)



Compound ID	R	Docking score
a	Benzimidazole	-8.1
b	Methylated benzimidazole	-8.2
c	Difluoro benzimidazole	-8.6

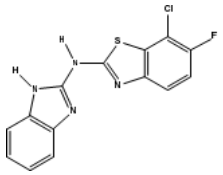
The standard drug Exemestane exhibited its binding within the active site of the target protein (Aromatase receptor) predominantly through hydrophobic and limited polar interactions. The molecule formed multiple hydrophobic contacts with amino acid residues such as Val 370, Phe 221, Trp 224, and Leu 477, indicating stabilization within a largely nonpolar binding pocket. Additionally, interactions with Ile 132 and Ile 133 further contributed to hydrophobic stabilization. Unlike the designed ligands, the standard drug displayed limited hydrogen bonding, with interactions mainly governed by van der Waals forces and shape complementarity. However, the presence of charged residues such as Arg 115 and Asp 309 suggests possible electrostatic contributions, including unfavorable or weak charge interactions, influencing the overall binding orientation.

In contrast, the first ligand (N-(1H-benzo[d]imidazol-2-yl)-7-chloro-6-fluorobenzo[d]thiazol-2-amine) demonstrated strong binding affinity characterized by extensive hydrophobic interactions with residues such as Val 370, Phe 430, Met 364, Met 446, and Leu 152 within the active pocket. The aromatic rings and halogen substituents (–Cl and –F) of the ligand contributed significantly to π–alkyl and van der Waals interactions. The interaction profile indicates that the ligand is deeply embedded within a hydrophobic cavity, with minimal involvement of hydrogen bonding, suggesting that binding is primarily driven by hydrophobic forces.

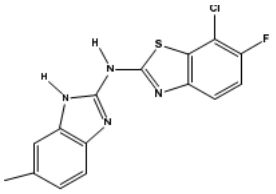
Similarly, the second ligand (7-chloro-6-fluoro-N-(6-methyl-1H-benzo[d]imidazol-2-yl)benzo[d]thiazol-2-amine) formed multiple hydrophobic interactions involving Phe 430, Val 370, Leu 152, Ile 442, Met 446, and Ala residues (Ala 438 and Ala 443) at various distances. Notably, this ligand also exhibited one conventional hydrogen bond with Cys 437, enhancing binding specificity compared to the standard drug. Furthermore, the ligand showed improved interaction diversity due to the presence of heteroatoms capable of forming polar contacts, thereby increasing its stabilization within the binding pocket.

The third ligand (7-chloro-N-(5,6-difluoro-1H-benzo[d]imidazol-2-yl)-6-fluorobenzo[d]thiazol-2-amine) displayed a more diverse interaction profile compared to the other ligands. In addition to multiple hydrophobic interactions with residues such as Val 370, Phe 430, Met 311, Met 303, Leu 152, and Ala residues, the ligand also formed hydrogen bonding interactions with Cys 437 and Ala 306. Moreover, the presence of aromatic rings facilitated π–π and arene–H interactions, further strengthening ligand binding. These interactions, along with favorable van der Waals contacts, indicate a more stable and energetically favorable binding mode relative to both the standard drug and other ligands.

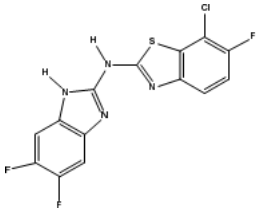
Overall, while the standard drug relies mainly on hydrophobic interactions with limited electrostatic contributions, the designed ligands exhibit enhanced interaction profiles, including additional hydrogen bonding and aromatic interactions. This suggests that the designed ligands may possess improved binding affinity and specificity, as the number and strength of hydrogen bonds, along with optimal interaction distances, are critical factors influencing ligand–receptor stability.



(a)

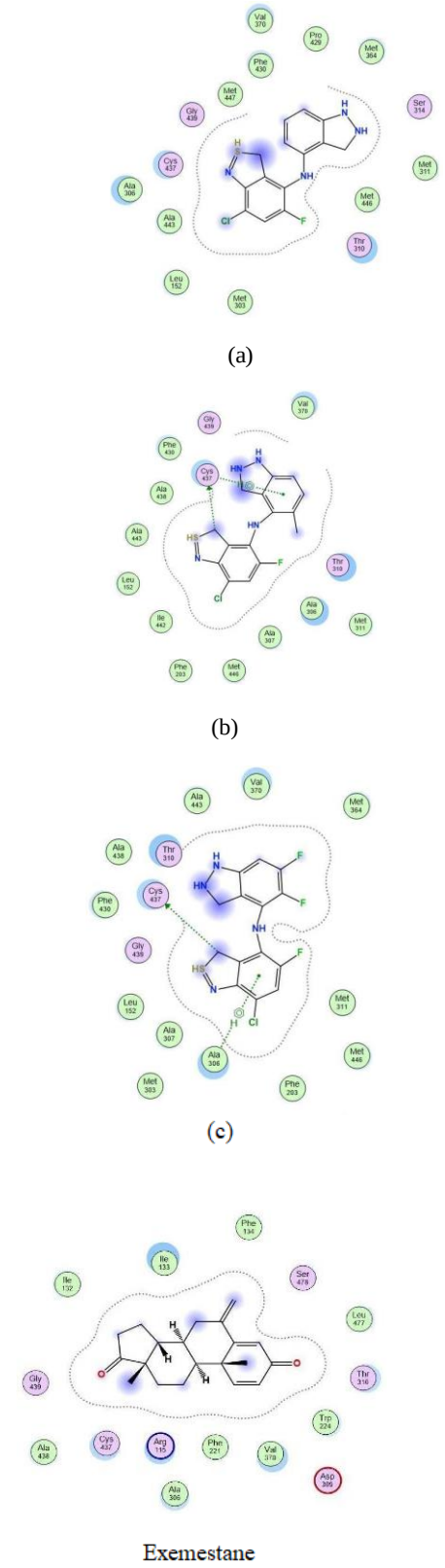


(b)



(c)

Fig 1. Molecular structures of compounds a, b and



(a)

(b)

(c)

Exemestane

Fig. 2 Docking of compounds a, b, c and Exemestane

3.2 ADME/Pharmacokinetics Prediction

The drug-likeness and drug-toxicity studies parameters are shown in Table 2 and Table 3.

In drug-likeness, the parameters like no of rotatable bonds, hydrogen bond acceptors, hydrogen bond donors, log P, and log S value as well as GI permeability are performed using SWISS ADME[15] No of rotatable bonds determines the flexibility of the compound to bind with its target. It should be less than 10 as per Veber's rule[17] for good oral bioavailability. Hydrogen bonding affects the molecule's solubility, permeability, and binding capacity. As per Lipinski's rule[18], hydrogen bond acceptors should be less than 10 and hydrogen bond donors should be less than 5. Log P stands for octanol-water partition coefficient. It should be less than 5 as per Lipinski's rule of 5. A log P value of more than 5 shows poor solubility, increased metabolism, and potential toxicity because of high lipophilicity. Log P value less than zero denotes poor absorption and permeability because of high hydrophilicity. Log S stands for aqueous solubility. Log S value greater than -4 indicates good solubility. As per the data in table 2, all the compounds are within the range of standard data and as they have high GI permeability, they can be formulated as oral dosage form as they would have good absorption in systemic circulation through GI wall.

Toxicity study is a very important parameter while developing a new drug moiety. A toxicity study was performed by the PROTOX III server. It indicates the possible toxicities of the molecule. As per the data denoted in table 3, there is very low hepatic toxicity[19] for all the novel derivatives, which indicates that all the novel derivatives are under the category of class IV[20] which is non-irritating and non-toxic compounds[21]. These results indicate that all the novel benzothiazole derivatives are safe to administer.

Table 2: Results of drug-likelines

Sr no	Code	MW g/mol	No of Rota-table bonds	H-bond Accept-ors	H-bond Donors	Log P	Log S	GI Permeability
1	a	318.7	2	3	2	3.96	5.39	High
2	b	332.7	2	3	2	4.33	5.68	High
3	c	354.7	2	5	2	4.86	5.69	High

Table 3. Results of toxicity studies

Sr no	Co-de	Hepato toxicity	Nephro-toxicity	Cardio-toxicity	Carcino-genicity	Muta genicity
1	a	Low	No	No	No	No
2	b	Low	No	No	No	No
3	c	Low	No	No	No	No

4. Conclusion

In the present research, the theoretical evaluation of binding affinities (kcal/mol) of some benzothiazole derivatives with Aromatase target was carried out in order to validate their potency. The molecular docking results showed a good docking score ranged from − 8.1 kcal/mol to – 8.6 kcal/mol signifying that the molecules can bind more tightly with the active site of the target. As per the results of drug likeness, all the derivatives are highly permeable through GI membrane therefore, oral dosage form can be developed and from the results of toxicity studies, all the drugs are under class IV i.e. non-toxic and non-irritating compounds.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates. CA Cancer J Clin. 2018;68(6):394–424.
2. Popaniya HS, Vaja PN, Tank CJ. Tyrosinase inhibition: A potent mechanism of action of plants used in treatment of Melasma. Asian Journal of Pharmaceutical Research. 2024;14(3):289-94
3. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. 2003;348:2431–2442.
4. MedlinePlus Genetics. CYP19A1 gene: cytochrome P450 family 19 subfamily A member 1.
5. Glubb DM, O'Mara TA, Shamsani J, Spurdle AB. CYP19A1 variation and circulating estradiol levels in postmenopausal women. Front Pharmacol. 2017;8:218.
6. Fabian CJ. The what, why and how of aromatase inhibitors. Int J Clin Pract. 2007;61(12):2051–2063.
7. Nardin S, Ruffilli B, Landolfo TL, et al. Aromatase inhibitors as adjuvant therapy in early breast cancer. Cancers (Basel). 2025;17(17):2726.
8. Thakare SD, Joshi RI, Burle PD, Bakane PV. Computer-aided drug design and molecular docking applications. IIP Series. 2026;6:26–44.
9. Sharmila B, Radhika M, et al. A comprehensive review of molecular docking: principles, methods and applications. IJPS J. 2024.
10. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability. Adv Drug Deliv Rev. 1997;23:3–25.
11. Bhagdev KN, Tank CJ. Design and evaluation of novel benzothiazole-benzimidazole hybrids as potential anticancer agents. Int J Drug Deliv Technol. 2026;16(45S):1372–82.
12. Becke AD. Becke's three-parameter hybrid method using the LYP correlation functional. J Chem Phys. 1993;98:5648–52.
13. Adeniji SE, Shallangwa GA, Arthur DE, Abdullahi M, Mahmoud AY, Haruna A. Quantum modelling and molecular docking evaluation of some selected quinoline derivatives as antitubercular agents. Heliyon. 2020;6:e03639.
14. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31:455–61.
15. Singh SP, Konwar BK. Molecular docking studies of quercetin and its analogues against human inducible nitric oxide synthase. SpringerPlus. 2012;1:69.
16. Ursu O, Rayan A, Goldblum A, Oprea TI. Wiley Interdiscip Rev Comput Mol Sci. 2011;1(5):760–81.
17. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45(12):2615–23.
18. Chen X, Li H, Tian L, Li Q, Luo J, Zhang Y. J Comput Biol. 2020;27(9):1397–406.
19. Ghosh S, Tripathi P, Talukdar P, Talapatra SN. World Sci News. 2019:35–51.
20. Hodge HC, Sterner JH. Am Ind Hyg Assoc Q. 1949;10(4):93–6.
21. Borkhataria CH, Sharma S, Vaja P, Tank C, Mori D, Patel K, Kyada A. Quality management, ethical considerations, and emerging challenges in genomics and biobanking: A comprehensive review. Clinica Chimica Acta. 2025 Mar 1;569:120161.