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Research Article

Design, Molecular Docking and Molecular Dynamic Simulation of New Heterocyclic Derivatives as Potential Anticancer Agents

Dheyaa Ali Abdulqader*, Monther Faisal Mahdi

Department of Pharmaceutical Chemistry Department, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

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Abstract

Background: Despite significant progress in the development of anticancer medications, obstacles such as drug resistance, poor efficacy, and excessive toxicity have significantly impacted the daily lives of cancer patients. Consequently, the search for highly selective, effective, and non-toxic molecules remains a major challenge for cancer researchers. ***Objective***: To utilize a computer program for evaluating new benzothiophene derivatives to investigate how they influence the estrogen-related receptor-gamma (ERRγ) active sites as anticancer agents. ***Methods***: The molecular docking method used the Cambridge Crystallographic Data Centre's (CCDC) Genetic Optimization for Ligand Docking (GOLD) tool. We used the Desmond modules of the Schrodinger 2023 to perform MDS on the derivative with the highest docking score. The Swiss ADME server then assessed our drugs' pharmacokinetic profile, which included how well they crossed the blood-brain barrier (BBB), bound to P-gp, and were bioavailable. ***Results***: The compounds were docked with the ERRγ crystal structure (2GPV) to assess their binding affinity to active sites. One of them earned a high score (102.62), and six compounds had a higher binding energy than the gold standard medication, tamoxifen. The molecular dynamic simulation analysis found that compound 1 closely matched the ERRγ based on RMSD and RMSF data. After examining the ADME study of practically active substances, they follow Lipinski's laws and other pharmacokinetic features. ***Conclusions***: These chemicals have the potential to act as precursors in the development of new anticancer medicines.

Keywords: ADME, Anticancer activity, Benzothiophene, ERRγ inhibitors, Molecular docking.

التصميم والالتحام الجزيئي والمحاكاة الديناميكية الجزيئية للمشتقات الحلقية غير المتجانسة الجديدة كمضاد محتمل للسرطان

الخلاصة

الخلفية: على الرغم من التقدم الكبير في تطوير الأدوية المضادة للسرطان، هناك عقبات عديدة مثل مقاومة الأدوية، ضعف الفعالية، والسمية المفرطة، التي تؤثر على الحياة اليومية لمرضى السرطان. وعليه فإن العثور على أدوية مضادة للسرطان انتقائية وفعالة وغير سامة يمثل تحديًا كبيرًا في أبحاث السرطان الحالية. **الهدف**: نقدم تقييمًا لسلسلة جديدة من مشتقات البنزوثيوفين لتحديد التأثير المضاد للسرطان في المواقع النشطة لمستقبلات جاما المرتبطة بالإستروجين (ERRγ). **الطرق**: استفادت طريقة الالتحام الجزيئي من برنامج التحسين الوراثي Ligand (GOLD)التابع لمركز كامبريدج للبيانات البلورية. تم إجراء MDS للمشتق الذي حصل على أفضل درجة التحام باستخدام وحدات Desmondفي Schrodinger 2023 وتم تقييم الملف التعريفي للحركية الدوائية لمركباتنا، بما في ذلك نفاذية BBB (حاجز الدم في الدماغ)، والتقارب لـP-gp ، والتوافر البيولوجي، باستخدام خادم ADME السويسري. **النتائج**: تم ربط مركباتنا الاثني عشر بالبنية البلورية ERRγ رمز بنك بيانات البروتين: 2GPVلتحديد مدى ارتباطها بالمواقع النشطة. أظهر أحد هذه المركبات درجة عالية (102.62) وستة مركبات لديها طاقة ربط أعلى من عقار تاموكسيفين المعياري. كشفت دراسة المحاكاة الديناميكية الجزيئية أن المركب 1 له توافق جيد مع ERRγ وفقًا لبيانات انحراف مربع متوسط الجذر (RMSD) وبيانات تقلب متوسط مربع الجذر (RMSF) وبعد تحليل دراسة ADME للمركبات النشطة فعليًا، تطابقوا مع قواعد ليبينسكي وغيرها من خصائص الحركية الدوائية. **الاستنتاج**: يمكن لهذه المركبات أن تعمل كمقدمة لتطوير أدوية جديدة مضادة للسرطان.

* ***Corresponding author***: Dheyaa A. Abdulqader, Department of Pharmaceutical Chemistry Department, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq; Email: dhiaa84pharma@gmail.com

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INTRODUCTION

Cancer is the second-leading cause of death globally and according to GLOBOCAN 2018, by 2040, estimated incidences would increase to 29.5 million [1]. In spite of the expanding antitumor agents that have evolved to date, breast cancer is a major type of cancer observed compared to other cancers in women, affecting approximately 2.1 million people every year [2]. From 2009 through 2018, along with an overview of recently

reported numbers globally, the incidence rate is clearly on the rise, which is indicative of aggressive screenings and detections [3]. The mortality rate has not increased at the same pace, suggesting better clinical management of breast cancer patients, but the numbers are still too high. While screenings and early diagnoses should still be a point of focus, particularly in developing and poor countries, more efforts are needed to improve the prognosis of patients diagnosed at a later stage [3]. Approximately 70% of all breast cancers (BC) express the estrogen receptor (ER), progesterone receptor (PgR), or both, and such tumors are considered hormone receptor-positive (HR+). In addition to testing for the presence of ER and PgR, testing for human epidermal growth receptor 2 (HER2) protein overexpression and/or HER2 gene amplification is also performed at the time of diagnosis, and these test results aid in informing treatment decisions [4]. The selective estrogen receptor modulator tamoxifen (Figure 1) has been widely used for more than 30 years as the first-line hormonal therapy and adjuvant therapy after surgery for ER-positive breast cancer patients.

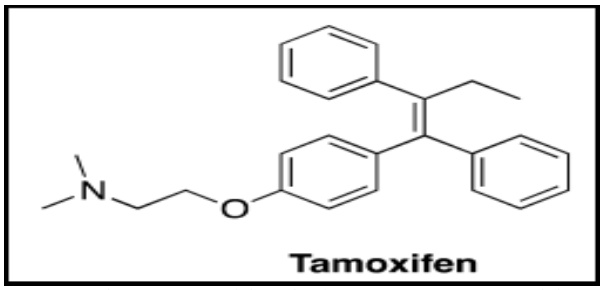


Figure 1: The structures of the selective estrogen receptor modulator tamoxifen.

Tamoxifen blocks ER-stimulated tumor growth in the breast, providing a 47% reduction in recurrence and a 26% reduction in mortality, as documented in a 5-year treatment clinical trial. Tamoxifen also acts as an ER agonist in bones, the uterus, and other tissues, which is beneficial for preventing bone demineralization in postmenopausal women [5]. Much attention has been paid to the role of ERRs in breast cancer, as they are orphan nuclear receptors closely related to ERs. ERRα expression in breast tumors is often high, and it is expressed in tumors with poor prognosis. In samples from various cohorts of patients with breast cancer, ERRα mRNA positively correlates with the expression of the oncogene ERBB2 and inversely correlates to that of ERα and PR, which are considered good prognostic markers for patients with breast cancer. The expression of ERRα mRNA and protein positively correlates with the coactivator amplified in breast cancer 1 (AIB1), also known as SRC-3 [6]. However, ERRα is able to act as both a transcriptional activator and repressor depending on the cellular context, promoting or inhibiting tumor growth in breast cancer [7]. In ER+ breast cancer cells, ERRα functions as a transcriptional repressor, interacting with corepressors and binding to negative EREs [8]. The estrogen-related receptor (ERR) family belongs to nuclear hormone receptors and consists of three closely related members (α, β, and γ). ERRs share significant homology to ERα at the DNA-binding domain and recognize the ERE, which indicates that ERRs modulate the actions of ERs. However, ERRs are not activated by known natural estrogens and are therefore classified as orphan receptors. ERRs can also bind to steroidogenic factor 1 (SF1)-binding elements within the promoter regions of various steroidogenic P450 genes, including aromatase [9]. Although the ERRs do not directly respond to b-estradiol, they can bind to functional estrogen response elements (EREs) in ER target genes such as lactoferrin and aromatase, suggesting a possible overlap between ERR and ER biology. Although natural ligands have not yet been described for the ERRs, two lines of evidence suggest that these receptors may be hormone-regulated [10]. Estrogens, belonging to the family of steroid hormones, are synthesized starting from cholesterol, transported inside the mitochondria and converted into pregnenolone, the precursor of all steroid hormones, which is then exposed to an extensive metabolism by the 17,20-hydroxylase lyase enzyme to give androstenedione (ASD). ASD is then converted into the two most common estrogens in the body, estrone (E1) and estradiol (E2), by the action of two enzymes: 17β-hydroxysteroid dehydrogenase and aromatase (CYP19A1). In particular, the latter, which belongs to the superfamily of cytochromes P450, converts ASD into E1 and testosterone (TST) into E2 [11]. The present study design and evaluates a new series of benzothiophene derivatives to determine their anticancer effect in the estrogen-related receptor-gamma (ERRγ) active sites.

METHODS

Protein receptor and ligand preparation

The crystal structure of epidermal growth factor receptor complexes with tamoxifen was obtained from the Protein Data Bank (PDB) under the code 2GPV. We removed the right ionization tautomeric states from the target protein structures, added hydrogen atoms, and eliminated water molecules to obtain amino acid residues. The structures of the ligand molecules are drawn using ChemDraw (version 22.0.022). We implemented a molecular mechanic force field in Chem3D (version 22.0.022) to reduce the energy of the twelve selected ligand molecules.

Docking procedures

The molecular docking method made use of the Cambridge Crystallographic Data Centre's (CCDC) Genetic Optimization for Ligand Docking (GOLD) program. ChemDraw, another piece of Cambridge-

created software, was also used. For this examination, we used v2022.3.0. The receptor was prepared for docking and the images were captured using the Hermes visualizer (version 2022.3.0, Cambridge, England) as part of the GOLD suite. The GOLD docking binding site consists of all protein residues within 10A of the reference ligands in the downloaded protein structure complexes. The number of produced poses was kept at ten, the top-ranked solution was kept as the default, and the early termination option was disabled. Chemscore kinase was used as a configuration guide. As a scoring function, the piecewise linear potential (ChemPLP) is employed. Finally, the findings were stored as mol.2 files [12]. ChemBioOffice (version 22.0.022) was used to display the chemical structures of the ligands. To perform ensemble docking, multiple distinct estrogen-related receptor proteins (1KVF, 2GPV, and 1S9P) were downloaded from the PDB database. Thus, the ERRγ protein crystal structure 2GPV was selected since it shows an interaction with tamoxifen. The ChemPLP fitness was employed as the scoring function in this study, which was designed using the Chemscore kinase. The final posture number was not altered; 10 was kept as the default; and the highest-ranked solution was designated the default. To learn how the ligands we designed interacted with the ERRγ protein's amino acid residues, we analyzed docking data. In this study, we considered the effects of docking position, binding free energy, and binding mode.

Molecular dynamic simulations

MDS was performed for the derivative with the best docking score using the Sibiolead Biocomputing cloud platform with the OPLS4 force field. To create a charge-neutral system for the protein-ligand complex, sodium ions were added, and 0.15 M sodium chloride was included to mimic the natural system. Utilizing the TIP3P solvent model, the system was produced. The simulation was run for 50 ns, with recording intervals of 50 ps for the trajectory. We used the NPT ensemble class and set the system energy to 1.2. The simulation was set to operate at 1.01325 bar and 300 k. We evaluated the simulated system after relaxation to create the simulation interaction diagram.

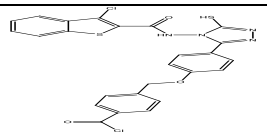
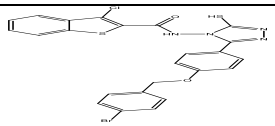
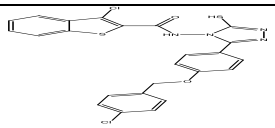
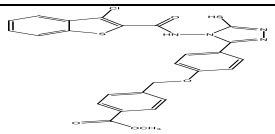
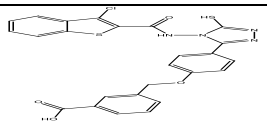
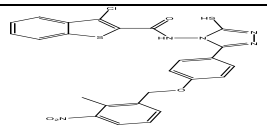
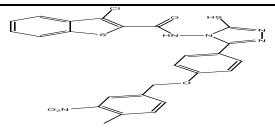
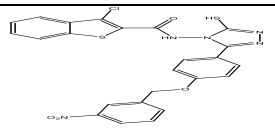
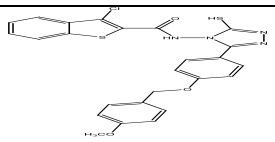
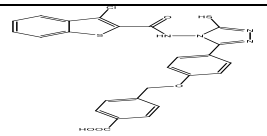
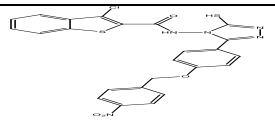
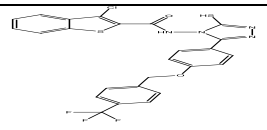
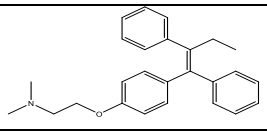
ADME procedure

The pharmacokinetic profile of our compounds, including their BBB (blood-brain barrier) permeability, affinity for P-gp, and bioavailability, was evaluated using the Swiss ADME server. To identify therapeutic candidates that exhibit optimal safety and promise to be given orally, a crucial step involves the exclusion of compounds possessing inadequate ADME (absorption, distribution, metabolism, and excretion) properties, which are prone to failure during subsequent stages of drug development [13]. The ligands were initially created using the ChemDraw software and subsequently exported as SMILE names through the utilization of the SwissADME tool. The polarity and lipophilicity of the compounds were evaluated using the BIOLED-Egg tool.

RESULTS

A genetic algorithm called GOLD was used to dock flexible ligands to protein binding sites, predicting the optimal molecular interaction between the expected compounds (1–12) and the active binding site of the ERRγ protein [14]. Examining the contact interactions between the protein's active binding sites and our compounds allowed us to determine the selectivity, affinity, and binding energies of the ligands for the ERRγ through docking. The ranking of the ERRγ inhibitory activity of compounds 1–12 and tamoxifen was determined based on their PLP fitness. The docking analysis revealed that several amino acid residues, including TYR 436, LYS 439, TRP 305, MET 306, LEU 268, ASP 273, ARG 316, VAL 313, GLU 275, ILE 310, VAL 444, ALA 272, CYS 269 and LEU 309 inside the active site of the ERRγ, engage in interactions with our final ligands through hydrogen bonding and short contacts. The docking result of the inhibitors against the ERRγ receptor is shown below in Table 1. To further confirm the interaction, the compound 1-2GPV complex was subjected to MDS analysis. Simulations of molecular dynamics (MD) are now an established technique that can be applied effectively to comprehend macromolecular ligand-receptor bindings. Also, unlike the more static molecular docking method, MD modeling does not ignore the fact that proteins change over time. The highest-scoring ligand was subjected to MD simulations to understand the evolution of receptor binding ability over time. The dynamic behavior of Comp 1-2GPV was studied and recorded for 50 ns. The stability of the protein-ligand complex was assessed by studying RMSD and RMSF values. The results showed that the ligand had an RMSD within an acceptable range of less than 2.1 Å, and the protein's RMSD was less than 2.8 Å in the complex state. The effects of the synthesized analogues on the ADME properties have been analyzed by the Swiss ADME server to diagnose the safer and potential drug candidate(s) and to eliminate compounds that may fail due to uncomplimentary ADME properties in the next phases of drug production. Figure 2 illustrates a representation of BOILED-Egg. Medications intended for oral administration must comply with Lipinski's rule of 5, which states that they should have a molecular weight of less than 500, a partition coefficient (o/w) of less than 5, fewer than 5 hydrogen bond donors, and fewer than 10 hydrogen bond acceptors. Furthermore, the drug must possess a polar surface area of less than 140 Å, as this is an essential property directly linked to its bioavailability. There exists an inverse relationship between the PSA levels and the oral bioavailability of the medicine.

Table 1: The estrogen related receptor active site docking score for several benzothiophene derivatives.

No.	Molecule structure	PLP Fitness	H-Bond	Short contact
1.		**92.77**	Tyr 436, Lys 439	Tyr 436, Trp 305, Met 306, Leu 268, Asp 273, Arg 316, Val 313
2.		**96.33**	Cys 269, Asp 273	Glu 275, Trp 305, Ile 310, Leu 268, Arg 316, Ala 272, Cys 269
3.		**99.93**	Cys 269	Ile 310, Trp 305, Met 306, Leu 265, Cys 269, Arg 316
4.		**102.62**	Lys 439, Tyr 436	Leu 265, Trp 305, Met 306, Leu 268, Cys 269, Phe 435, Lys 439, Arg 316, Ile 310, Tyr 436
5.		**100.03**	Cys 269, Lys 439, Tyr 436	Lys 439, Trp 305, Cys 269, Glu 275, Met 306, Val 313, Arg 316
6.		**100.94**	Tyr 436, Lys 439, Asp 273, Cys 269, Tyr 326	Ile 310, Tyr 436, Glu 275, Arg 316, Met 306, Val 313, Cys 269, Ala 272
7.		**99.91**	Lys 439	Glu 275, Trp 305, Met 306, Lys 439, Cys 269, Ile 310, Leu 309
8.		**98.6**	Lys 439, Cys 269, Tyr 436	Cys 269, Ile 310, Tyr 436, Trp 305, Ala 272, Met 306, Leu 271, Val 313arg 316, Lys 439, Leu 309, Trp 439
9.		**96.24**	Cys 269, Lys 439, Tyr 436	Leu 268, Arg 316, Trp 305, Asp 273, Cys 269, Tyr 436lys 439
10.		**88.11**	Lys 439, Cys 269, Tyr 326	Lys 439, Trp 305, Cys 269, Met 306, Tyr 436, Ile 310, Arg 316
11.		**93.8**	Lys 439, Tyr 362, Tyr 436, Cys 269	Lys 439, Cys 269, Leu 265, Met 306, Thr 266, val 444, Trp 305
12.		**100.69**	Cys 269, Lys 439	Cys 269, Trp 305, Met 306, Ile 310, Arg 316, Tyr 436
Tamoxifen		**97.07**	Arg 316, Tyr 326, Glu 275, Asp 273	Tyr 326, Leu 309, Met 306, Leu 345, Ala 431, Ile 310

To enhance the oral bioavailability, all substances must undergo passive absorption, which is facilitated by having a topological polar surface area (TPSA) of less than 140 Å [15].

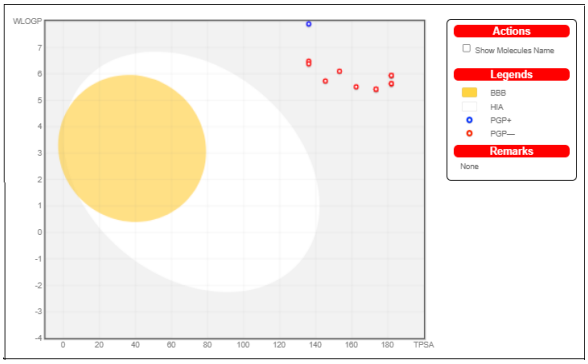


Figure 2: BOILED-Egg for benzothiophene derivatives compounds (1-12).

DISCUSSION

We have selected twelve of the best compounds, all of which exhibit good binding energies to the ERR active sites. As shown in Table 1, compound (4) has the highest PLP fitness of 102.62 and the strongest H-bonding with amino acids. The binding energies of compounds 3, 5, 6, 7, 8, and 12 are higher than those of the standard drug tamoxifen. This helps explain why the PLP has fitness values of 99.93, 100.03, 100.94, 99.91, 98.6 and 100.69, in that order. Other compounds (1, 2, 9, 10, and 11) have slightly lower binding energies than tamoxifen (92.77, 96.33, 96.24, 88.11, and 93.8, respectively), and they bind to the same amino acids as the standard drug tamoxifen binds to them with excellent results. As illustrated in Table 1, all the designed ligands showed strong interactions with key amino acids in the binding site as compared with the standard drug Tamoxifen. Figure 3 displays how the standard drug Tamoxifen interacts with key amino acids in the binding site. The best PLP fitness is shown by compounds 4, 6, and 12, which can be seen in Figures 4, 5, and 6. Table 1 also shows these compounds.

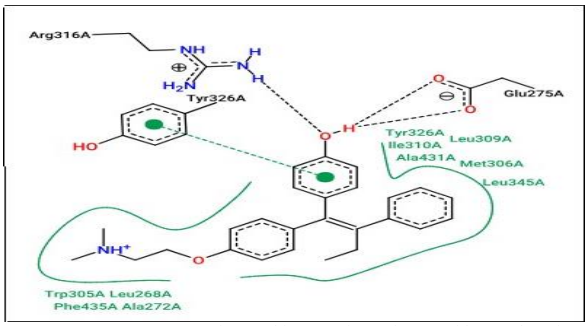


Figure 3: 2D representations of interaction of tamoxifen and amino acids in ERRγ active sites.

Compound 4, which has the highest docking score, forms two H-bonds with Lys 439 and Tyr 436 residues, as well as short contacts with Leu 265, Trp 305, Met 306, Leu 268, Cys 269, Phe 435, Lys 439, Arg 316, Ile 310, and Tyr 436 (Figure 4).

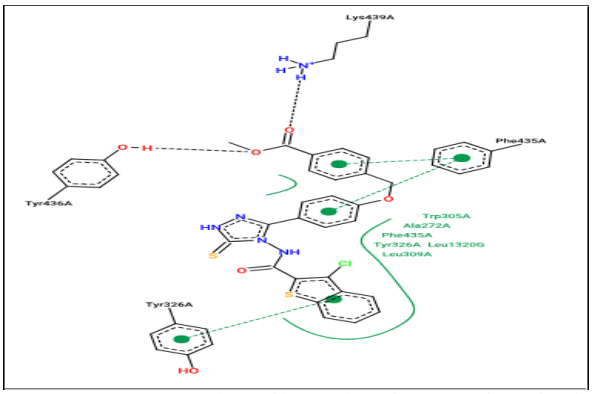


Figure 4: 2D representations of interaction of compound 4 and amino acids in ERRγ active sites.

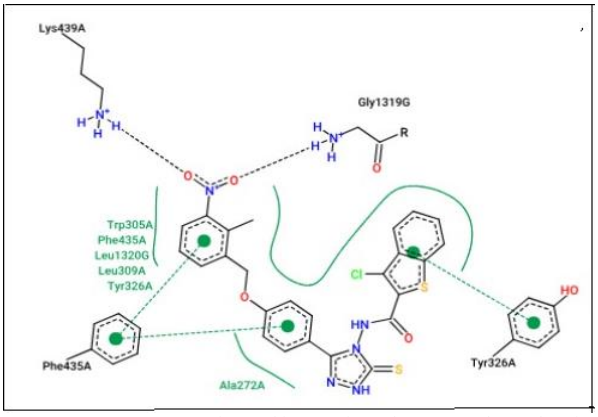


Figure 5: 2D representations of interaction of compound 6 and amino acids in ERRγ active sites.

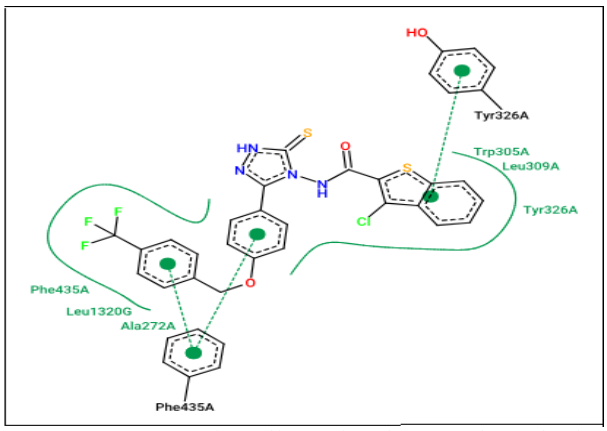


Figure 6: 2D representations of interaction of compound 12 and amino acids in ERRγ active sites.

The previously mentioned interactions have enhanced the capabilities of new compounds, designating them as anticancer agents with greater effectiveness and binding affinity [16]. Furthermore, the MDS analysis revealed a stable ligand and protein in the complex throughout the simulation time, as depicted in Figure 7 of the RMSD results. Additionally, the majority of the protein had an

RMSF of less than 1.0 Å, according to the RMSF analysis, which further demonstrates a stable protein structure, as shown in Figure 8 [17].

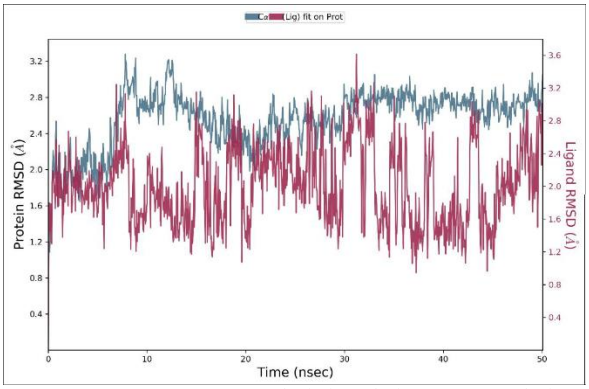


Figure 7: Root-mean-square deviation during MDS analysis of compound 1 –2GPV complex.

Analysis of synthesized analogues using the Swiss ADME server has demonstrated that compound 12 Point, colored blue, is a molecule predicted to be a substrate of the P-glycoprotein (PGP+) and hence actively pumped up from the brain or to the gastrointestinal lumen. Compounds 1–11 were predicted to be non-substrates of the P-glycoprotein (PGP), with the relevant point highlighted in red.

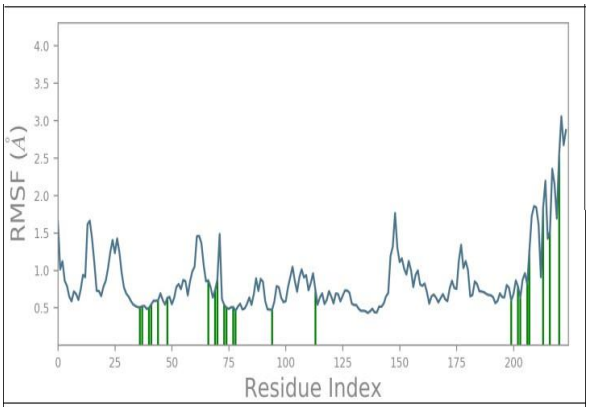


Figure 8: Root means square fluctuations, during MDS analysis of compound 1 –2GPV complex.

Furthermore, Table 2 reveals that all our compounds defy Lipinski's rules, are incapable of oral absorption due to their high molecular weight, and require delivery via an alternative route [18].

Study limitations

This work requires experimental validation for the activity of these designed compounds as anticancer.

Table 2: ADME study results for different benzothiophene derivatives

Compounds	TPSA	Water solubility	G.I Absorption	BBB Permeability	Lipinski	Veber
1	153.15 Å²	Poorly Soluble	Low	No	No	No
2	136.08å²	Poorly Soluble	Low	No	No	Yes
3	136.08å²	Poorly Soluble	Low	No	No	Yes
4	162.38å²	Poorly Soluble	Low	No	No	No
5	173.38å²	Poorly Soluble	Low	No	No	No
6	181.90å²	Poorly Soluble	Low	No	No	No
7	181.90 Å²	Poorly Soluble	Low	No	No	No
8	181.90 Å²	Poorly Soluble	Low	No	No	No
9	145.31 Å²	Poorly Soluble	Low	No	No	No
10	173.38 Å²	Poorly Soluble	Low	No	No	No
11	181.90 Å²	Poorly Soluble	Low	No	No	No
12	136.08 Å²	Poorly Soluble	Low	No	No	Yes

TPSA: topological polar surface area, GI: gastro intestinal tract.

Conclusion

The tested compounds show increased anticancer activity and binding affinity. The designed ligands have excellent pharmacokinetic and physicochemical characteristics but do not match Lipinski's principles. The data from the molecular dynamic simulation demonstrated the stability of the Compound 1-2GPV complex and the preservation of critical protein-ligand interactions throughout the simulation period. The results also showed that compound 1 had acceptable RMSD and RMSF values and worked well with estrogen-related receptors as a ligand. Finally, these compounds can serve as precursors for the development of new anticancer agents. As a result, to determine their effectiveness, side effects, and toxicity profile, all proposed compounds must go through extensive in vivo and in vitro studies.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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