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In Silico Molecular Docking & ADMET Study Of Benzothiazole Fused With 1,3,4-Oxadiazole Derivatives For Anti-Cancer Activity

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ABSTRACT
Currently, the primary technique for evaluating potential ADME, harmful effects of medication candidates is animal testing. An alternate strategy is to use in silico prediction techniques, which rationalise preclinical medication development in order to cut costs, time, and animal experimentation. In present study, we used Molegro virtual docker 6.0, Swiss ADME, ProTox II and PASS online web server for the prediction of best derivative for anticancer activity. A disorder called cancer is characterised by uncontrollably proliferating cells, which can spread or signal other health problems. More than one hundred distinct forms of cancer influence people. Some cancers encourage fast cell proliferation, although others cause cells to divide and grow slowly. Some diseases, such as leukemia, create visible tumours, whereas others, such as breast cancer. In present work new Benzothiazole fussed 1,3,4-oxadiazoe derivatives were predicted and evaluate for in silico anti-cancer study. The protein (PDB ID: 3ERT) was chosen as the target since it contains ER-alpha and is listed in the Protein Data Bank. Five analogs SPZ1, SPZ3, SPZ6, SPZ10 & SPZ11 were showed very good mol-dock score pasturing in the middle -123.14 to -165.72 whereas both standard drugs Tamoxifen and Raloxifen showed mol-dock score -146.08 and -165.06 respectively which is comparatively lower than hypothetical synthesize compounds. Log P data of predicted analogs were founded to be less than five except SPZ2, SPZ4, SPZ7, SPZ8, SPZ9 & SPZ12 (Log P=5.05 to 5.99), reveal good membrane permeable. It was discovered that SP1, SP3, SP6, and SP11 have an active mutagenicity with a probability of 0.51. The immune and cytotoxicity of the all the predicted derivatives was found to be inactive.

Keywords Benzothiazole, Molecular docking, ADME, Toxicity, Anticancer activity

Introduction

According to Gabr *et al,.* (2020), cancer is the second leading cause of death worldwide and a significant public health concern. Cancer is one of the most deadly illnesses in the world because it is caused by unchecked cell proliferation, aberrant cell division, and the conversion of normal cells into malignant ones (Ranjan *et al*., 2022; Sharma *et al*., 2020). Most malignancies still have extremely low overall and disease-free survival rates, despite enormous efforts to discover viable treatment options that have not yet produced satisfying outcomes. Thus, there is still a pressing need to find safer and more effective anticancer drugs (Liu *et al*., 2020).

Nowadays, chemotherapy is a viable option for stopping the growth of tumour cells or eliminating them through a variety of methods. A number of obstacles, including drug resistance, low bioavailability and solubility, and toxicity to normal cells, make the development of new safe, effective chemotherapeutic agents for the treatment of cancer difficult (Meguid *et al*., 2021). According to published research, people can develop a wide range of carcinogenic disorders, including leukaemia, colon cancer, lung cancer, breast cancer, and prostate cancer. Out of all the many kinds of cancer, breast cancer is thought to be the leading cause of mortality for women globally (Harisha *et al*., 2020). Because targeted medicines are highly selective for tumour cells, they may be used more broadly and with less damage to normal cells. Compared to conventional chemotherapy, they are typically better tolerated. Therefore, the rationally based design of novel anticancer drugs benefits from the discovery of molecular targets implicated in cell death,proliferation, and malignancies (Liu *et al*., 2020).

Heterocycles are a significant family of chemicals that are widely found in essential bioactive compounds (Kaushik and Chahal 2020). Heterocyclic chemistry is generally regarded as one of the important areas of pharmaceutical industry research. Sulfur-bearing scaffolds have gained popularity recently because of their many therapeutic uses in the field of medicinal chemistry. Among all, the benzothiazoles depicted in Figure 1 are thought to be the most adaptable fused heterocyclic compounds. They have a prominent role in the medical area and have been linked to a number of biologically, naturally occurring, and pharmaceutically active chemicals (Vemuluri *et al*., 2024). At the forefront of drug discovery is the design and synthesis of bioactive heterocycles containing nitrogen (Aljuhani *et al*., 2021). Medicinal chemists and biochemists have focused on incorporating the benzothiazole pharmacophore moiety into anticancer drug design in order to clinically realise the concept of combined anticancer therapies or multi-acting drugs, based on the distinctive properties listed in Table 1 (Chen *et al*., 2020).

Heterocyclic compounds, or benzothiazoles, exhibit a wide variety of biological functions. Benzothiazole derivatives have been shown in several studies to have a wide range of properties, including as antibacterial, anti-inflammatory, antifungal, anticancer, antidiabetic, anticonvulsant, antiviral, antitubercular, antimalarial, and antihelmintic effects. A

few commercially available medications with the benzothiazole nucleus Figure 2. Specifically, among the favoured structures in medicinal chemistry are 2-substituted benzothiazoles. Certain derivatives of benzothiazoles with two substituents have been assessed recently as possible anticancer agents (Liu *et al*., 2020; Costa *et al.,* 2024; Gu *et al*., 2024; Goya-Jorge *et al*., 2020; Morsy *et al*., 2020). Several ben-zothiazole compounds were shown to have a distinct cytotoxicity profile, particularly when it came to MCF-7 cell lines (Abd El-Meguid *et al*., 2022).

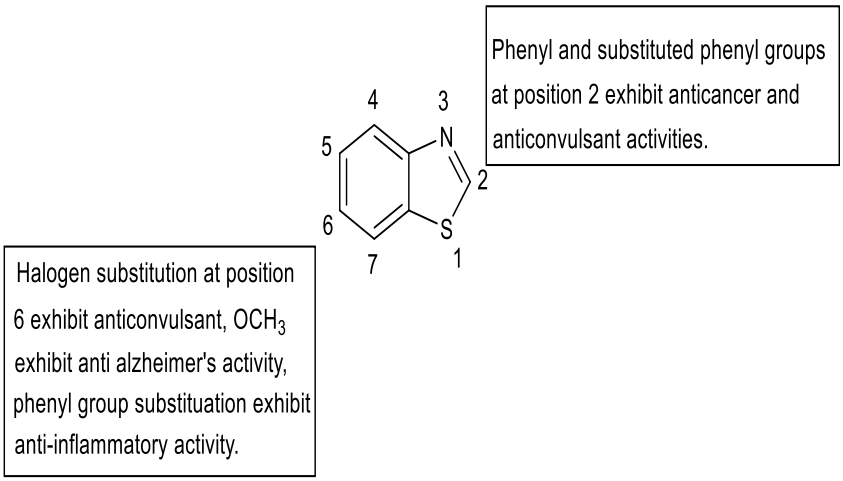

Figure 1. Chemical structure of Benzothiazole

Table 1. Physico-chemical properties of benzothiazoles

Property	**Descriptor**
Molecular Formula	C_7H_5NS
Molecular Weight	135.1863
B.P.	227-228 °C
M.P.	2 °C
Density	1.644 g/ml
Physical appearance	Colorless, slightly viscous liquid
Density	1.246 g/ml at 20 °C
Refractive index	163 at 20 °C
Vapour pressure	0.07mm Hg at 20 °C
Log *p*	2.01
Molar Refractivity	40.57 ± 0.3 cm^3
Surface Tension	54.2 ± 3.0 dyn/cm
Solubility	Slightly soluble in water, Highly soluble in ethanol, diethyl ether and carbon disulphide; soluble in acetone.
Reactivity	React with aldehydes & ketone to generate hydroxy carbonyl compound Not suitable for use with potent oxidising agents.
Stability	N-H = 3344cm^{-1} stretching C-H = 3025cm^{-1} stretching C=N = 1630cm^{-1} stretching
IR data	C-S = 1690cm^{-1} stretching

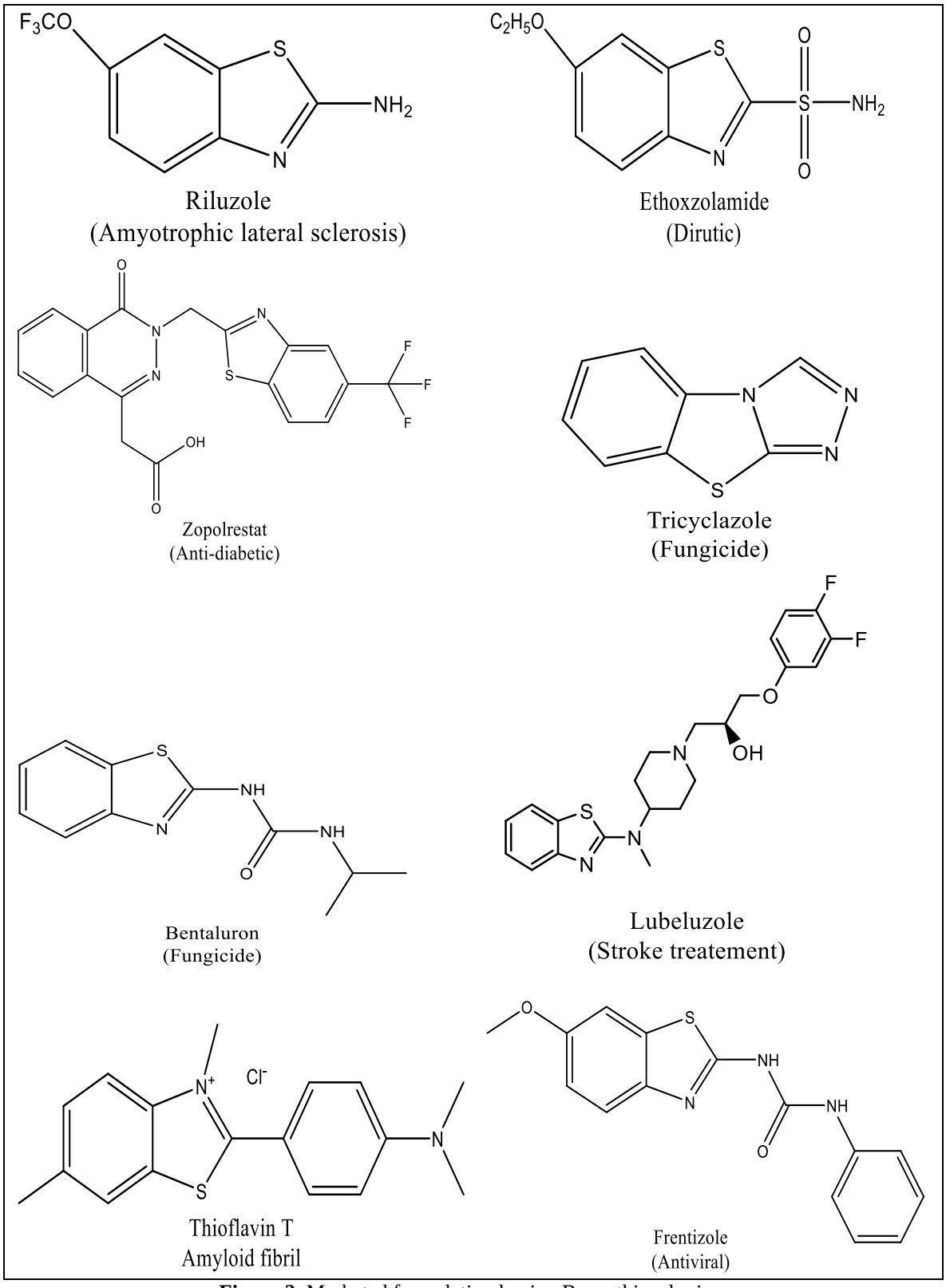

Figure 2. Marketed formulation having Benzothiazole ring

Methodology

Molecular modeling by using molegro virtual docker

Especially in the pharmaceutical industry, molecular docking studies have grown to be highly significant instruments in the drug design and discovery process. According to Govindaiah *et al.*, (2021) these techniques have demonstrated efficacy in identifying novel targets for drug development and may also be employed to connect biological outcomes,

which facilitates a more comprehensive comprehension of the mechanism of action. In order to anticipate the binding mechanism, molecular docking simulates ligand binding to a target receptor, usually the active site of a protein or enzyme. Predicting the ideal binding conformation, or pose, of the ligand within the binding site is the primary goal. It is an affordable method for drug creation that offers enhanced accuracy and reliability when identifying a molecule's binding sites (Godfrey *et al.,* 2023). A ligand is a tiny molecule that interacts with protein binding sites in a variety of mutually conforming configurations that can lead to binding. Molecular docking studies are now one of the most difficult parts of computer-aided drug discovery procedures. Molecular docking is widely utilised in contemporary drug design to comprehend drug-receptor interaction, which aids in the prediction of numerous organic compounds' potential medical uses (Harisha *et al.,* 2020).

In-Silico bioactivity prediction by using Swiss ADME software

The positive or negative effects of a medicine on the human body are explained by its bioactivity. It is contingent only upon meeting the ADME requirements. Therefore, in addition to being active, a chemical molecule has to have the right ADME qualities in order to be a good medication candidate (James and others, 2024). Using the Swiss ADME online programme, the pharmacokinetic characteristics of the hypothetical drugs were evaluated for the Absorption, Distribution, Metabolism, and Excretion (ADME) research in order to predict their oral bioavailability, adhering to Lipinski's rule of five. A newly created molecule must meet certain requirements in order to be absorbed orally: molecular weight <500, Log P (octanol-water partition coefficient) <5, number of rotatable bonds ≤10, hydrogen bond donors ≤5, and topological polar surface area ≤160. Drug candidates who violate more than one of these guidelines will have trouble absorbing nutrients orally. Using topological polar surface area (TPSA) and the formula % Abs=109−[0.345×TPSA], the percentage of absorption (% Abs) was determined (Bhutani et al., 2019). After selecting the "Calculation of Molecular Properties and Prediction of Bioactivity" tab, the SMILES of each of the 12 compounds were typed into the box. Following the instruction to "Predict Bioactivity," the results were tallied and shown in Table 2 (James *et al.,* 2024).

Toxicity Prediction by using ProTox II

Currently, the primary technique for evaluating potential harmful effects of medication candidates and cosmetics is animal testing. An alternate strategy is to use in-silico prediction techniques, which rationalise preclinical medication development in order to cut costs, time, and animal experimentation. Here, we forecast rodent oral toxicity using ProTox, a web server. It is estimated that the chances of drug candidates becoming commercialised pharmaceuticals are just 8% when they enter clinical trials, and that toxicities account for 20% of late-stage drug development failures. Numerous benefits arise from using computational predictions during the medication development process. They may be used at an early stage of the drug development process, which reduces the need for in vitro and in vivo research and saves time (Drwal *et al.,* 2014).

In recent years, attention has been focused on the development and optimisation of alternative techniques, such as in vitro experiments and in silico predictions (Basketter *et al*., 2012). The purpose of in silico toxicity models is to supplement the current in vitro toxicity approaches in order to anticipate the toxicity effects of chemicals while reducing the amount of time, money, and animal testing required. It may also be assessed qualitatively, using binary (active or inactive) for certain cell types and assays or indication areas such heptotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity, as well as quantitatively using LD50 (lethal dosage) values (Banerjee *et al*., 2018). The toxicity of synthetic derivatives (benzothiazole fused with 1,3,4-oxadiazoles) was investigated using the ProTox-II. ProTox-II is a free virtual laboratory available online that predicts a small molecule's toxicity by comparing its similarities to known dangerous chemicals. Each compound's SMILES string was copied individually and submitted. The expected median fatal dosage (LD50) in mg/kg weight, toxicity class, prediction accuracy, and average similarity will all be displayed on the result page, along with the three dangerous chemicals that are most similar to each other among the dataset's known rat oral toxicity values. After downloading the evaluation findings as a PDF file, the scores were calculated. This technique was used to predict AMES toxicity and rat oral acute toxicity scores. The boxes pertaining to carcinogenicity and mutagenicity were checked before to submitting for "Search." The order to "Start Tox Prediction" was issued when the molecule was verified. Calculations were made for the expected lethal dosage, 50% (LD50), toxicity class, likelihood of carcinogenicity, and mutagenicity scores. Table 5 tabulates the attributes. Higher a compound's toxicity, the lower its anticipated toxicity class (James *et al*., 2024).

Biological evaluation through PAAS Online Software

Several hundreds of biological activities based on SAR analysis were predicted through PASS online software e.g. - MOA, mutagenicity, teratogenicity, embryo toxicity, pharmacological & side effects. The maximum sharpness value indicates that algorithms and chemical caption worn in PASS software have extremely stable structure-activity relationships and accurate predictions. When PASS software results are compared with another method implemented in this area, Benchmark demonstrated that results collected from PASS software are in strong alignment (Lagunin *et al*., 2000).

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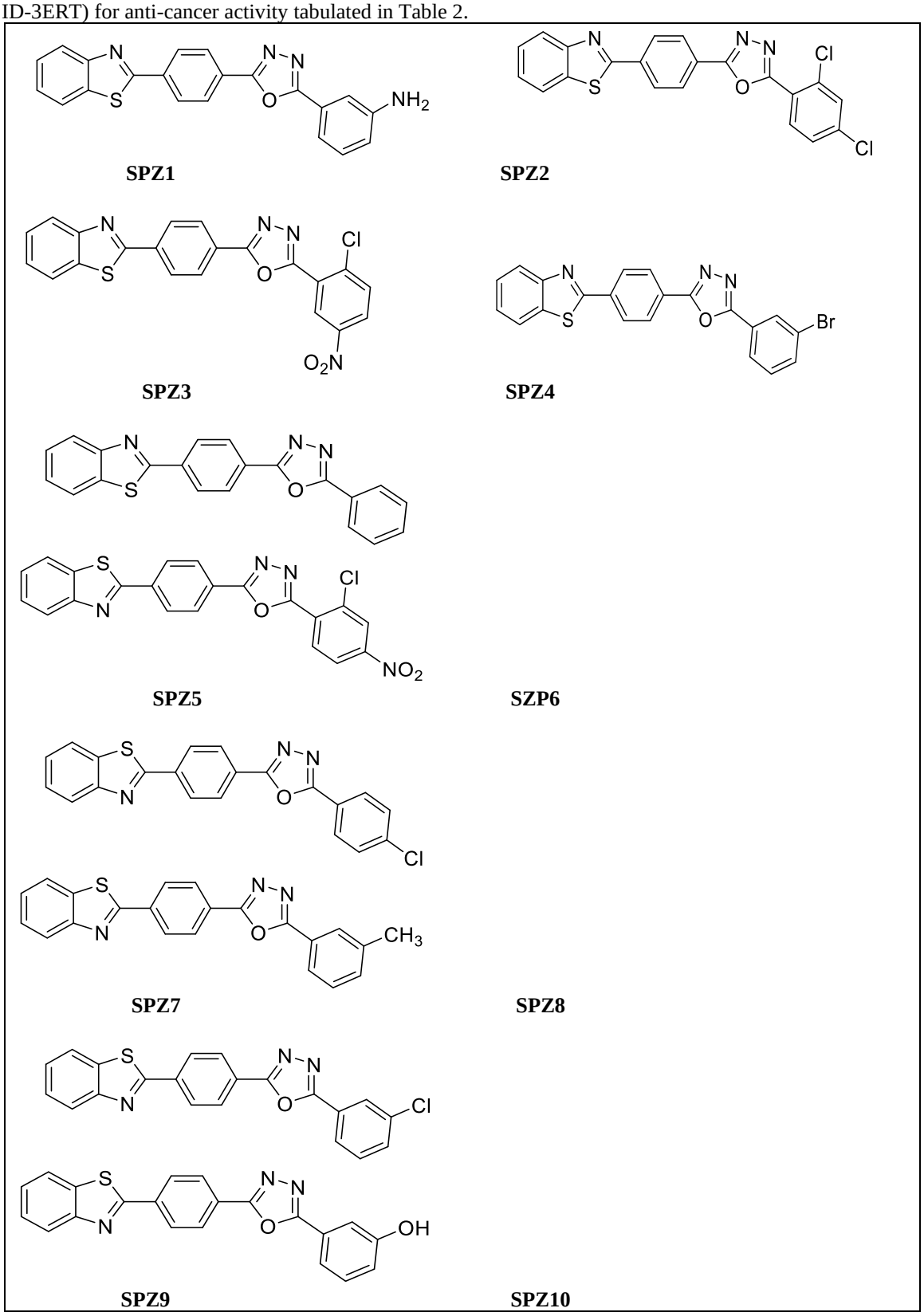
Results

Compounds selection and ligand preparation

The hypothetical compounds shown in Figure 3 were selected based on literature. The ligand molecules were prepared through Marvin Sketch version 5.11.0 and then molecules converted to 3D structure and added explicit hydrogen's. The MDL Molfile (*.mol) format of structure were used for docking studies into the workspace of Molegro Virtual Docker 6.0. On the basis of literature data, we selected 50 hypothetical compounds. The docking studies were done by using (PDB ID-3ERT) for anti-cancer activity tabulated in Table 2.



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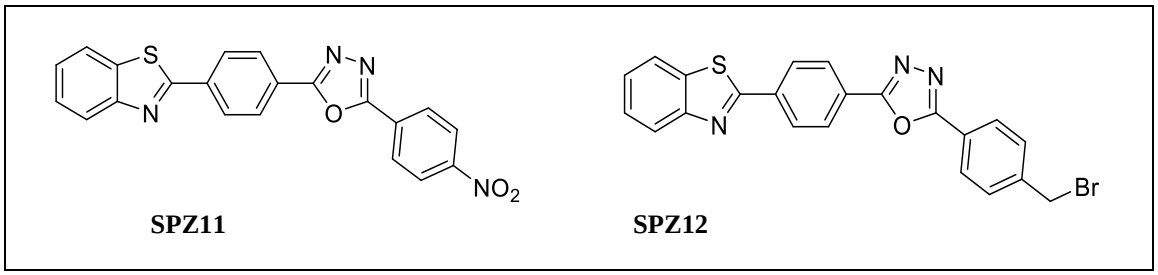

Figure 3. Predicted compounds based on literature

Table 2. Using the free edition of Molegro Virtual Docker 6.0, ligand-receptor interaction of benzothiazoles on PDB ID: (3ERT) with standard pharmaceuticals Tamoxifen and Raloxifen

Compound No.	Amino acid interaction with the H-bond (Å)	Number of hydrogen bonds	Mol. dock mark	Re-rank mark
Tamoxifen	O-Thr347 (3.41)	1	-146.08	-115.12
Raloxifen	O-Glu353 (3.14); O-Arg394 (2.87); O-Gly521 (3.31); O-His524 (3.17); O-Gly420 (3.20)	5	-165.06	-132.75
Internal ligand (OHT-600)	O-Arg394 (2.61); O-Glu353 (3.06); O-Thr347 (3.06)	3	-158.10	-126.02
SPZ1	O-Glu353 (2.84); O-Arg394 (2.82); O-Thr347 (3.11)	3	-165.72	-131.39
SPZ2	N-Thr347 (2.51); N-Thr347 (3.40)	2	-127.62	-101.65
SPZ3	N-Cys530 (2.88); N-Thr347 (2.58); N-Thr347 (3.31)	3	-128.78	-108.78
SPZ4	N-Thr347 (2.56); N-Thr347 (3.52)	2	-123.62	-100.27
SPZ5	N-Thr347 (2.58); N-Thr347 (3.55)	2	-119.18	-95.56
SPZ6	N-Thr347 (2.39); N-Thr347 (3.32); O-Cys530 (2.70); N-Cys530 (3.33)	4	-133.99	-104.16
SPZ7	N-Thr347 (3.38); N-Thr347 (2.50)	2	-123.65	-91.55
SPZ8	N-Thr347 (2.57); N-Thr347 (3.54)	2	-125.97	-99.80
SPZ9	N-Thr347 (2.57); N-Thr347 (3.56)	2	-126.11	-99.46
SPZ10	N-Thr347 (2.51); N-Thr347 (3.49); O-Leu525 (2.93)	3	-125.04	-101.32
SPZ11	N-Thr347 (2.59); N-Thr347 (3.58); O-Cys530 (2.67); N-Cys530 (3.41)	4	-129.36	-87.66
SPZ12	N-Thr347 (2.49); N-Thr347 (3.42)	2	-128.14	-98.84

Pictures showing Ligand–receptor interaction between PDB ID (3ERT) with predicted compounds

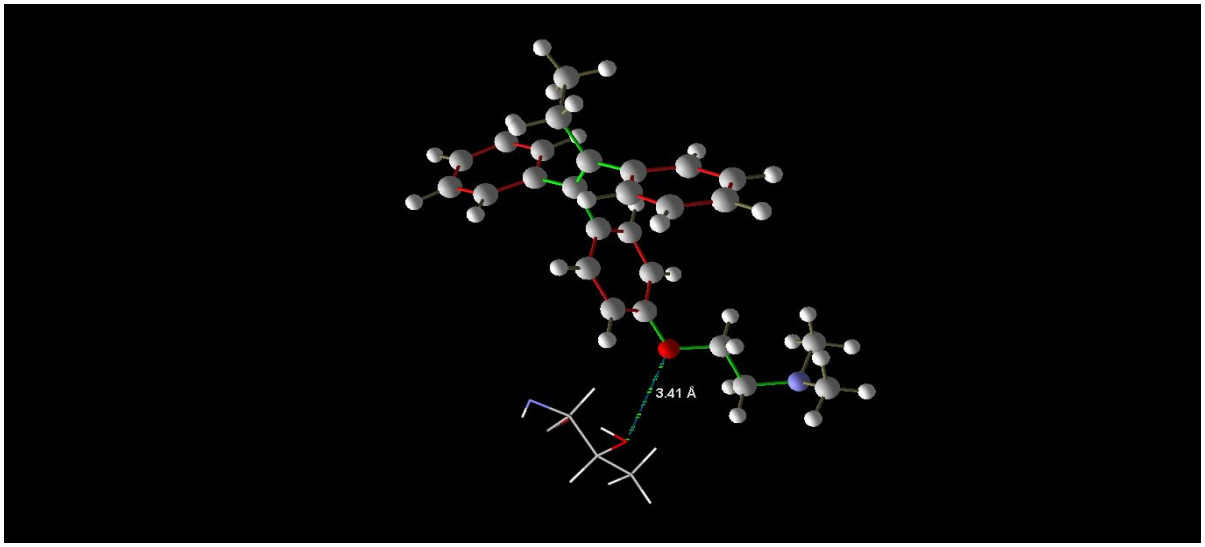

Figure 3. Interaction of reference drug Tamoxifen into PDB: 3ERT. It has Mol dock score -146.08 and formed 1 hydrogen bond shown as blue lines, between O-Thr347 with bond length (3.41 Å)

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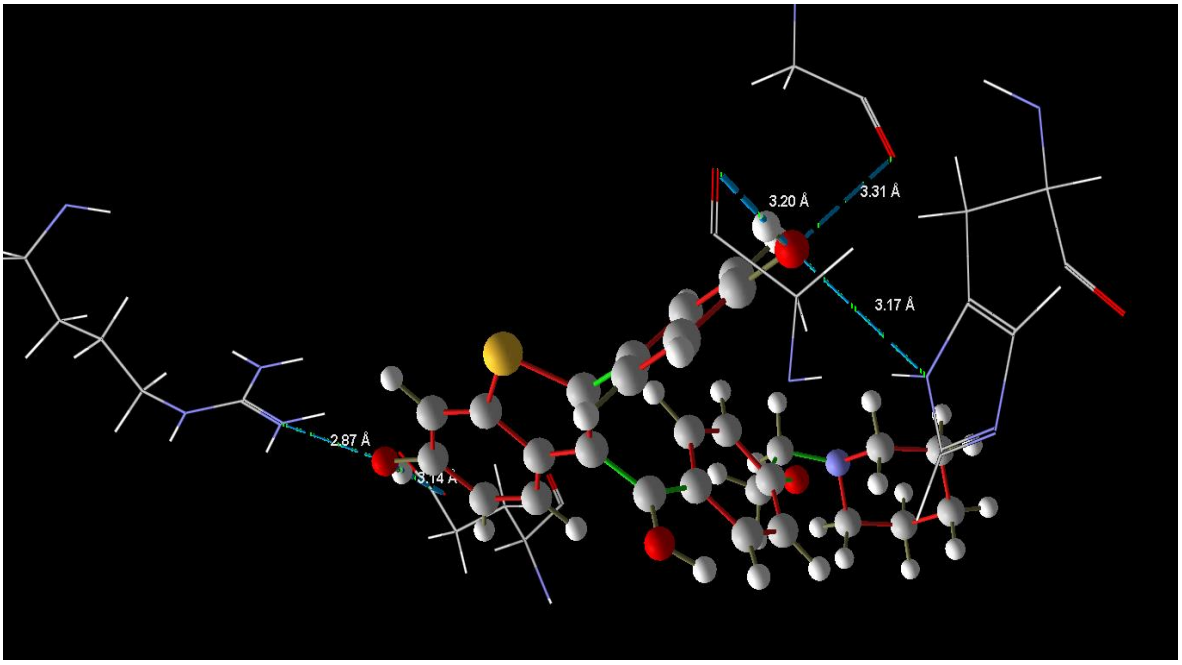

Figure 4. Interaction of reference drug Raloxifen with PDB: 3ERT. It has Mol dock score -165.06 and formed 5 hydrogen bond shown as blue lines, between O-Glu353 with bond length (3.14 Å), O-Arg394 with bond length (2.87 Å), O-Gly521 with bond length (3.31 Å); O-His524 with bond length (3.17 Å) and O-Gly420 with bond length (3.20 Å)

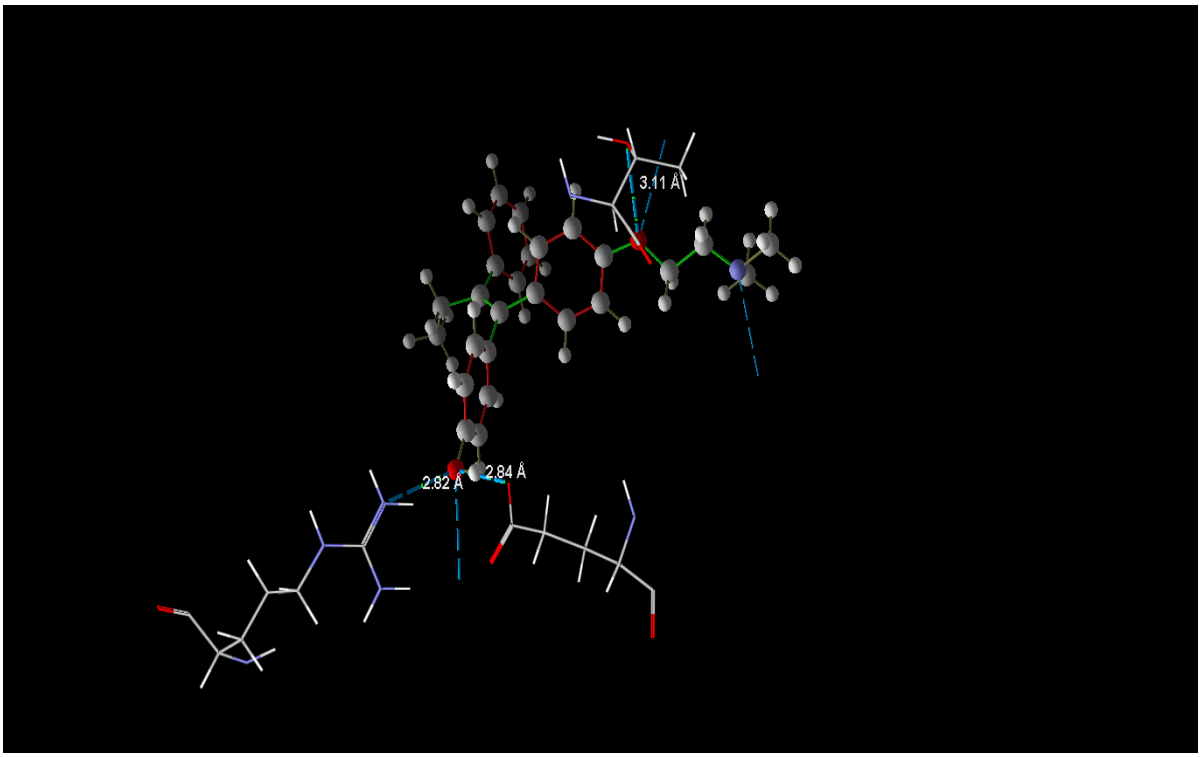

Figure 5. Interaction of analog-SPZ1 with PDB: 3ERT. It has Mol dock score -165.72 and formed 3 hydrogen bond shown as blue lines, between O-Glu353 with bond length (2.84 Å), O-Arg394 with bond length (2.82 Å) and O-Thr347 with bond length (3.11 Å)

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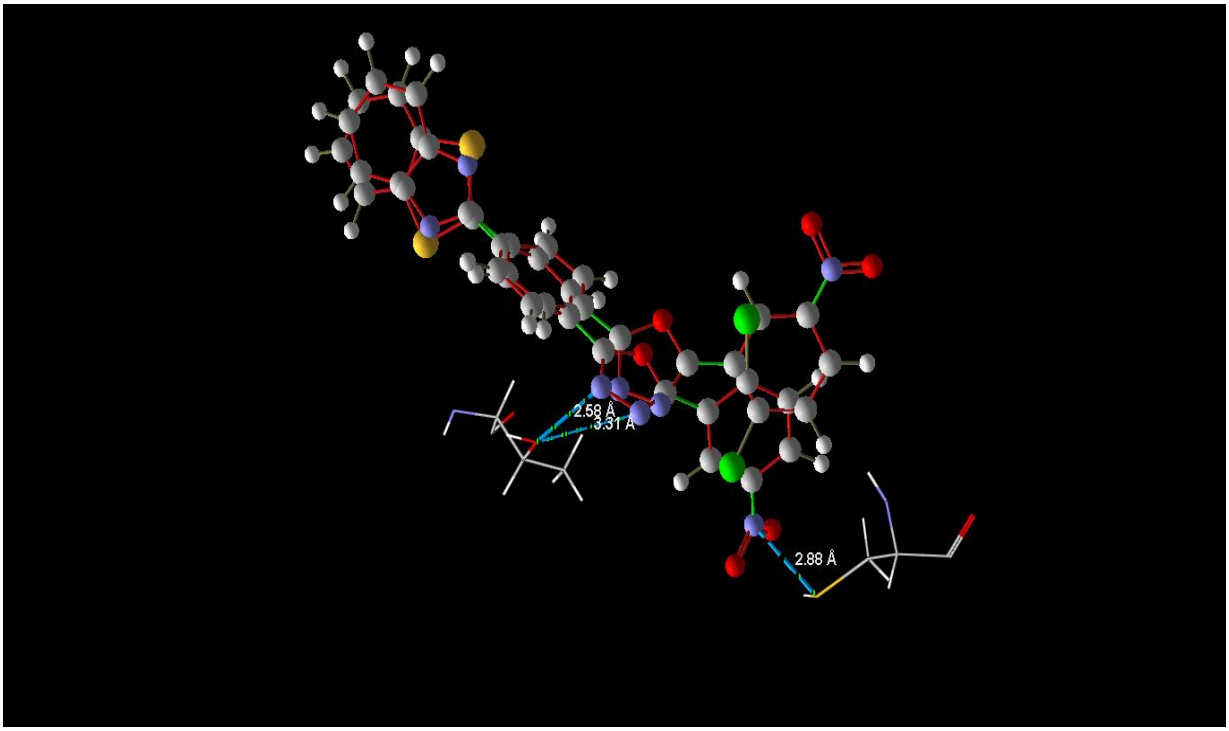

Figure 6. Interaction of analog-SPZ3 with PDB: 3ERT. It has Mol dock score -128.78 and formed 3 hydrogen bond shown as blue lines, between N-Cys530 with bond length (2.88 Å), N-Thr347 with bond length (2.58 Å) and N-Thr347 with bond length (3.31 Å)

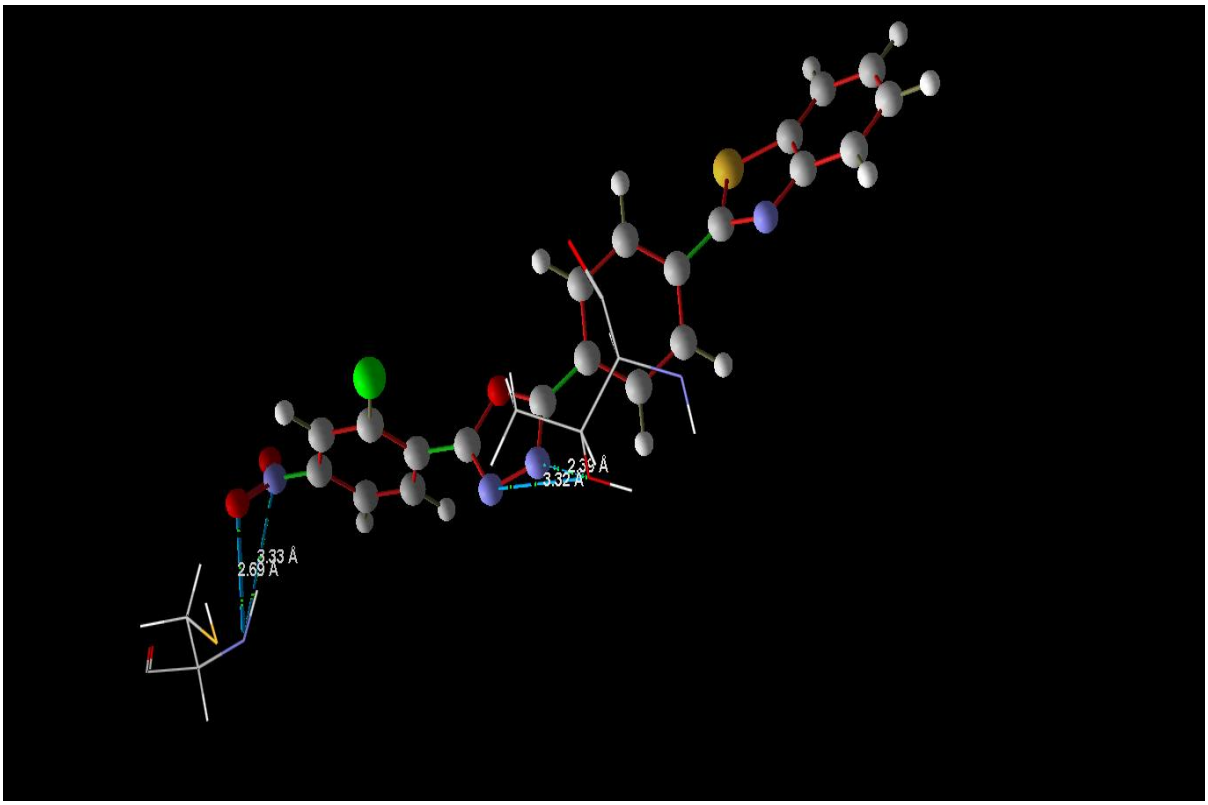

Figure 7. Interaction of analog-SPZ6 with PDB: 3ERT. It has Mol dock score -133.99 and formed 4 hydrogen bond shown as blue lines, between N-Thr347 with bond length (2.39 Å), N-Thr347 with bond length (3.32 Å), O-Cys530 with bond length (2.70 Å). and N-Cys530 with bond length (3.33 Å)

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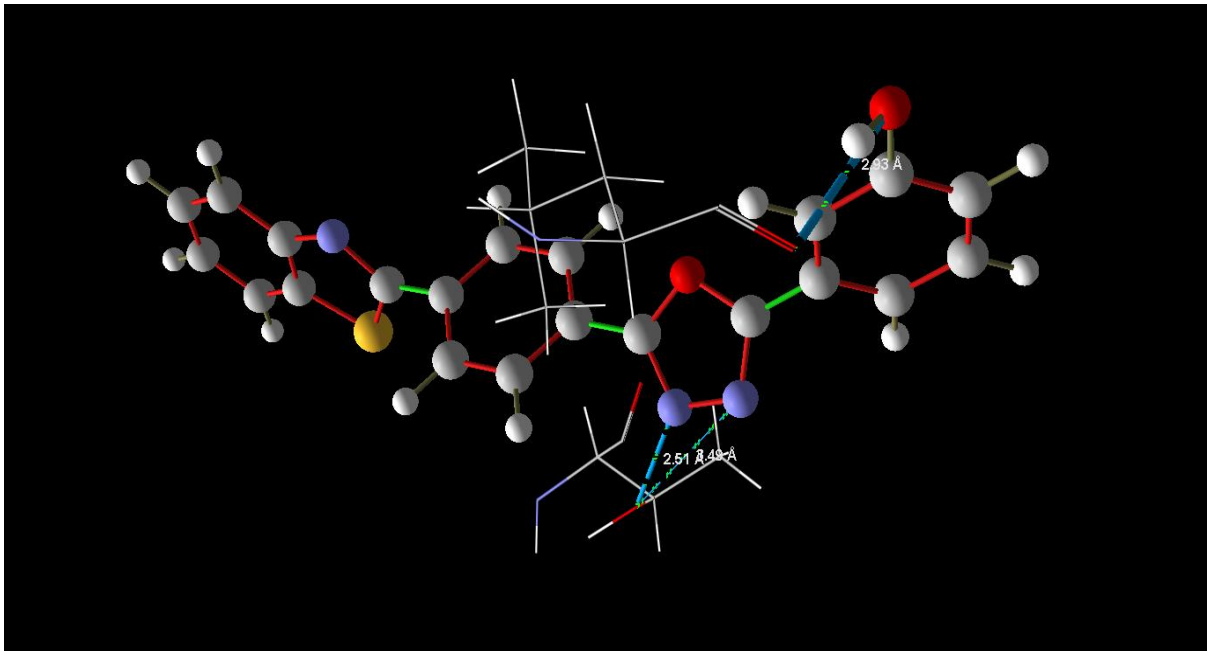

Figure 8. Interaction of analog-SPZ10 with PDB: 3ERT. It has Mol dock score -125.04 and formed 3 hydrogen bond shown as blue lines, between N-Thr347 with bond length (2.51 Å), N-Thr347 with bond length (3.49 Å) and O-Leu525 with bond length (2.93 Å)

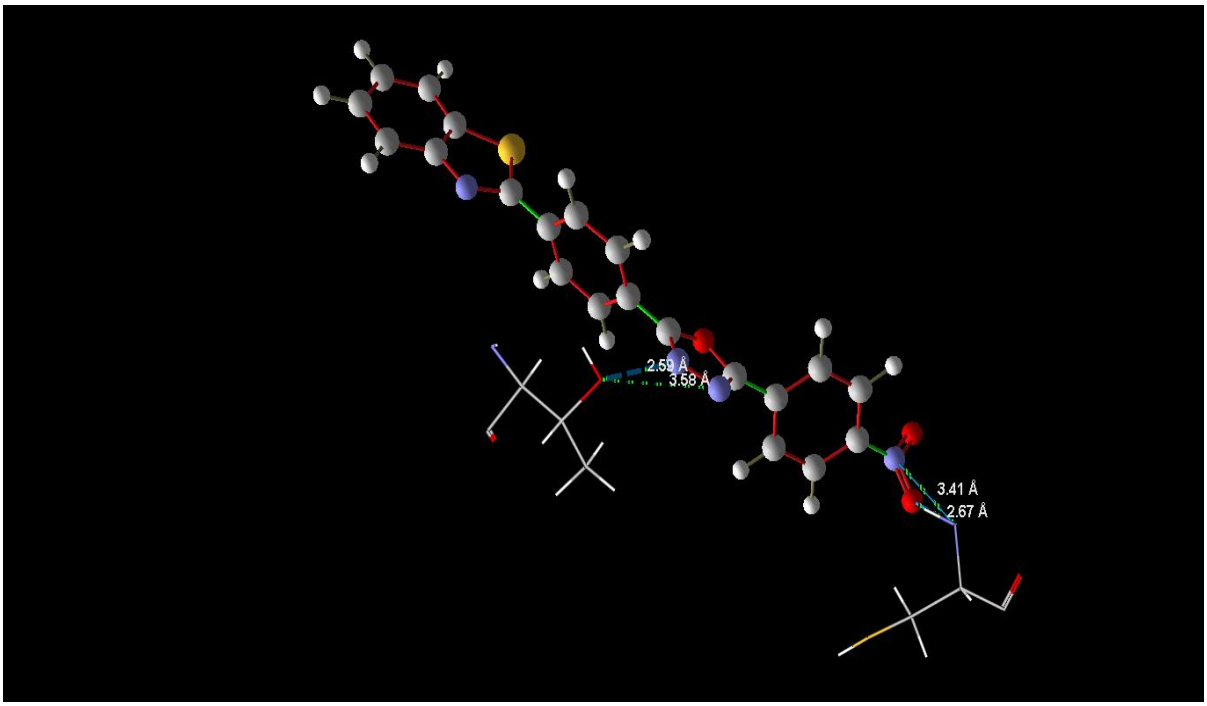

Figure 9. Interaction of analog-SPZ11 with PDB: 3ERT. It has Mol dock score -129.36 and formed 4 hydrogen bond shown as blue lines, between N-Thr347 with bond length (2.59 Å), N-Thr347 with bond length (3.58 Å), N-Cys530 with bond length (3.41 Å) and O-Cys530 with bond length (2.67 Å)

Physicochemical Properties

This section compiles the simple molecular formula as well as physical parameters such as polar surface area (PSA) of projected derivatives, count of certain atom types, molecular weight (MW), and molecular refractivity (MR). Using the fragmented method known as topological polar surface area (TPSA), the PSA is computed while taking phosphorus and sulphur into account as polar atoms. In several models and guidelines, this has shown to be an effective descriptor for rapidly estimating some ADME features listed in Table 3, particularly those related to biological barrier crossing, such as absorption, violation, and synthetic accessibility.

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Table 3. ADME study of predicted compounds

Compound	GI absorbtion[1]	TPSA[2] (A°)	n-rotb[3]	MW[4]	miLog Po/w[5]	n-OHNH[6]	n-ON[7]	n violation	Synthetic accessibility
Rule				**<500**	**<5**	**<5**	**<10**	**≤1**	
Tamoxifen	Low	12.47	8	371.51	5.77	0	2	1	3.01
Raloxifen	High	98.24	7	473.58	5.05	2	5	0	3.66
SPZ1	High	106.07	3	370.43	4.50	1	4	0	3.23
SPZ2	Low	80.05	3	424.30	5.97	0	4	1	3.18
SPZ3	Low	125.87	4	434.86	4.65	0	6	1	3.35
SPZ4	High	80.05	3	434.31	5.60	0	4	1	3.15
SPZ5	High	80.05	3	355.41	5.00	0	4	1	3.11
SPZ6	Low	125.87	4	434.86	4.64	0	6	0	3.29
SPZ7	High	80.05	3	389.86	5.52	0	4	1	3.10
SPZ8	High	80.05	3	369.44	5.33	0	4	1	3.12
SPZ9	High	80.05	3	389.86	5.52	0	4	0	3.12
SPZ10	High	100.28	3	371.41	4.64	1	5	0	3.80
SPZ11	High	125.87	4	400.41	4.24	0	6	0	3.25
SPZ12	High	80.05	4	448.34	5.66	0	4	1	3.31

GI absorbtion[1], Topological polar surface area[2], Number of rotable bonds[3], Molecular weight[4], Log of water partition coefficient[5], Number of hydrogen bond donors[6], Number of hydrogen bond acceptors[7]

Pro-tox-II predictor

Input parameter

The ProTox-II's user interface is simple to use and self-explanatory. The user has two options for predicting possible toxicities associated with a chemical structure: typing the compound's name or inserting its SMILES (Simplified Molecular-Input Line-Entry System) string. With the aid of the chemical editor (https://www.chemdoodle.com/), the user also has the option to sketch the chemical structure.

LD50

The globally harmonised system of classification was used to evaluate the compounds based on the upper threshold for high toxicity: LD50 less than 500 mg/kg indicates high toxicity, LD50 500 to 1000 mg/kg indicates moderate toxicity, and LD50 1000 to 2000 mg/kg indicates low toxicity (Navarro et al., 2021).

Toxicity Class

The toxicity of a substance increases with decreasing class. Five classes may be distinguished based on acute toxicity: class I is extremely toxic, class II is hazardous, class III is moderately toxic, class IV is mildly toxic, and class V is almost non-toxic (Yadav et al., 2017).

Cytotoxicity

For the purpose of screening substances that may result in both desired and undesirable cell damage—the latter being the case in the case of cancer cells—cytotoxicity prediction is crucial (Zhang et al., 2014), (Ahamad et al., 2023).

Carcinogenicity

Carcinogens are substances that have the ability to cause cancers or raise their occurrence (Kroes et al., 2004).

Mutagenicity

Mutagens are substances that result in aberrant genetic mutations, such as alterations in a cell's DNA (Ames et al., 1973). (James et al., 2024).

Hepatotoxicity

In the biochemical processes of metabolism, digestion, detoxification, and drug excretion from the body, the liver plays a pivotal and crucial function.Additionally, the liver serves as the main location for the metabolism of exogenous and endogenous chemicals (e.g., medications and poisons). Biotransformation is the process that changes lipophilic materials into hydrophilic ones so they may be eliminated later. The liver controls the level of plasma hormones and is a primary site of hormone catabolism (Moriles and others, 2024).

Immunotoxicity

According to Wang et al. (2022), immunotoxicity refers to a test substance's capacity to either inappropriately stimulate the immune system, which can result in allergies or autoimmune illnesses, or inhibit the immune system, which can raise the risk of infection or tumour disease.

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Table 4. Toxicity prediction of the predicted compounds

Compound	Predicted LD50 (mg/Kg)	Predicted Toxicity class	Average Similarity (%)	Predicted Accuracy (%)	Hepto toxicity	Carcinogenycity	Immuno toxicity	Muto genicity	Cyto toxicity
Tamoxifen	1190	4	100	100	Active	Inactive	Active	Inactive	Inactive
Raloxifen	1000	4	46.58	54.26	Inactive	Inactive	Inactive	Inactive	Inactive
SPZ1	1500	4	55.75	67.38	Active	Active	Inactive	Active	Inactive
SPZ2	1500	4	53.74	67.38	Active	Inactive	Inactive	Inactive	Inactive
SPZ3	2940	5	49.66	54.26	Active	Active	Inactive	Active	Inactive
SPZ4	1500	4	54.33	67.38	Active	Inactive	Inactive	Inactive	Inactive
SPZ5	1500	4	58.16	67.38	Active	Active	Inactive	Inactive	Inactive
SPZ6	1500	4	49.92	54.26	Active	Active	Inactive	Active	Inactive
SPZ7	1500	4	56.29	67.38	Active	Inactive	Inactive	Inactive	Inactive
SPZ8	1500	4	56.53	67.38	Active	Active	Inactive	Inactive	Inactive
SPZ9	1500	4	55.89	67.38	Active	Inactive	Inactive	Inactive	Inactive
SPZ10	1500	4	54.96	67.38	Active	Inactive	Inactive	Inactive	Inactive
SPZ11	1500	4	53.48	67.38	Active	Active	Inactive	Active	Inactive
SPZ12	1500	4	54.99	67.38	Active	Active	Inactive	Inactive	Inactive

Abbreviations: LD50, lethal dose, 50%

Prediction by using PASS online software

1. Open the PASS online software.
2. Click on prediction activity option for obtaining the biological action spectrum of stuff.
3. Send a Mol file already prepared with Chem Draw Professional.
4. The total numbers of chemical descriptors were obtained from selection of 'predicted results' with window shown in table 7 (Lagunin *et al*., 2000)

Where,

Pa = Probability of activity

Pi = Probability of inactivity

Thresholds which were to be chosen = Pa > Pi; Pa > 30%; Pa > 50% and Pa > 70%

Possibility of activity chosen = **Pa** > **Pi(**(Sadym et al., 2003), (Stepanchikova *et al.*, 2003).

Table 7. Biological activity spectrum by using PASS online software

Sr. No.	Activity	Pa	Pi
Tamoxifen	Antineoplastic (breast cancer)	0.817	0.004
	Estrogen antagonist	0.781	0.003
	Antineoplastic	0.690	0.028
	Antiinflammatory	0.384	0.014
Raloxifen	Estrogen antagonist	0.892	0.003
	Antineoplastic (breast cancer)	0.525	0.017
	Antineoplastic (uterine cancer)	0.296	0.005
	Antineoplastic enhancer	0.290	0.032
	Antineoplastic	0.285	0.162
	Antineoplastic (lymphoma)	0.162	0.089
SPZ1	Transcription factor STAT3 inhibitor	0.722	0.004
	Transcription factor inhibitor	0.628	0.005
	Focal adhesion kinase 2 inhibitor	0.609	0.003
	Alzheimer's disease treatment	0.512	0.028
	Apoptosis antagonist	0.456	0.005
	Antimycobacterial	0.413	0.036
	Autoimmune disorders treatment	0.390	0.059
	Antiinflammatory	0.412	0.089
	I kappa B kinase 2 inhibitor	0.285	0.004
	Interleukin agonist	0.210	0.053
	Epidermal growth factor receptor kinase inhibitor	0.179	0.028
	Tumour necrosis factor antagonist	0.155	0.076
SPZ2	Transcription factor STAT3 inhibitor	0.750	0.004
	Transcription factor STAT inhibitor	0.728	0.004
	Alzheimer's disease treatment	0.562	0.008
	Transcription factor inhibitor	0.535	0.010
	Antiinflammatory	0.457	0.070
	Autoimmune disorders treatment	0.385	0.061

	Interleukin 5 antagonist	0.166	0.011
	I kappa B kinase 2 inhibitor	0.141	0.005
SPZ3	Transcription factor STAT3 inhibitor	0.771	0.004
	Transcription factor STAT inhibitor	0.730	0.004
	Focal adhesion kinase 2 inhibitor	0.571	0.004
	Alzheimer's disease treatment	0.420	0.025
	Antiinflammatory	0.345	0.126
	Autoimmune disorders treatment	0.289	0.107
	Interleukin 5 antagonist	0.186	0.008
	Antineoplastic (pancreatic cancer)	0.258	0.097
	I kappa B kinase 2 inhibitor	0.098	0.010
	Tumour necrosis factor alpha antagonist	0.134	0.062
SPZ4	Transcription factor STAT inhibitor	0.858	0.003
	Transcription factor STAT3 inhibitor	0.855	0.003
	Transcription factor inhibitor	0.710	0.004
	Focal adhesion kinase 2 inhibitor	0.479	0.011
	Antineoplastic (pancreatic cancer)	0.299	0.059
	Epidermal growth factor receptor kinase inhibitor	0.241	0.017
	Antineoplastic (breast cancer)	0.280	0.061
	Antiinflammatory	0.330	0.136
	Autoimmune disorders treatment	0.289	0.289
	I kappa B kinase 2 inhibitor	0.164	0.005
	Antineoplastic (sarcoma)	0.207	0.050
	Estrogen beta receptor agonist	0.084	0.012
	Interleukin 5 antagonist	0.100	0.043
SPZ5	Transcription factor STAT3 inhibitor	0.816	0.003
	Transcription factor STAT inhibitor	0.814	0.003
	Transcription factor inhibitor	0.648	0.004
	Alzheimer's disease treatment	0.611	0.005
	Focal adhesion kinase 2 inhibitor	0.565	0.004
	Antiinflammatory	0.518	0.052
	Autoimmune disorders treatment	0.468	0.035
	I kappa B kinase 2 inhibitor	0.367	0.004
	Epidermal growth factor receptor kinase inhibitor	0.155	0.039
	Tumour necrosis factor alpha release inhibitor	0.143	0.085
	Antineoplastic (bladder cancer)	0.149	0.135
	Estrogen-related receptor alpha antagonist	0.052	0.047
SPZ6	Transcription factor STAT3 inhibitor	0.800	0.003
	Transcription factor STAT inhibitor	0.769	0.004
	Focal adhesion kinase 2 inhibitor	0.550	0.005
	Antiinflammatory	0.351	0.122
	Autoimmune disorders treatment	0.304	0.098
	Interleukin 5 antagonist	0.198	0.007
	Antineoplastic (pancreatic cancer)	0.268	0.087
	I kappa B kinase 2 inhibitor	0.112	0.008
	Tumour necrosis factor alpha antagonist	0.152	0.049
	Antineoplastic (bladder cancer)	0.158	0.113
	Antineoplastic (sarcoma)	0.159	0.132
SPZ7	Transcription factor STAT3 inhibitor	0.823	0.003
	Transcription factor STAT inhibitor	0.811	0.003
	Transcription factor inhibitor	0.627	0.005
	Alzheimer's disease treatment	0.543	0.009
	Antiinflammatory	0.494	0.059
	Apoptosis antagonist	0.434	0.005
	Autoimmune disorders treatment	0.423	0.049
	Epidermal growth factor receptor kinase inhibitor	0.156	0.038
	Antineoplastic (sarcoma)	0.169	0.107
	Antineoplastic (breast cancer)	0.173	0.124
	Tumour necrosis factor alpha antagonist	0.116	0.085

SPZ8	Transcription factor STAT3 inhibitor	0.827	0.003
	Transcription factor STAT inhibitor	0.821	0.003
	Transcription factor inhibitor	0.679	0.004
	Antiinflammatory	0.504	0.056
	Focal adhesion kinase inhibitor	0.455	0.010
	Apoptosis antagonist	0.441	0.005
	Autoimmune disorders treatment	0.444	0.042
	Interleukin 5 antagonist	0.140	0.016
	Antineoplastic (breast cancer)	0.190	0.101
	Epidermal growth factor receptor kinase inhibitor	0.117	0.064
	Tumour necrosis factor alpha antagonist	0.140	0.094
	Transcription factor NF kappa B inhibitor	0.112	0.082
SPZ9	Transcription factor STAT3 inhibitor	0.816	0.003
	Transcription factor STAT inhibitor	0.799	0.003
	Transcription factor inhibitor	0.615	0.005
	Antiinflammatory	0.485	0.062
	Apoptosis antagonist	0.401	0.007
	Autoimmune disorders treatment	0.406	0.054
	I kappa B kinase 2 inhibitor	0.275	0.004
	Epidermal growth factor receptor kinase inhibitor	0.149	0.042
	DNA directed RNA polymerase inhibitor	0.154	0.079
	Antineoplastic (sarcoma)	0.173	0.098
	Antineoplastic (breast cancer)	0.152	0.135
SPZ10	Transcription factor STAT3 inhibitor	0.798	0.003
	Transcription factor STAT inhibitor	0.795	0.004
	Transcription factor inhibitor	0.664	0.004
	Focal adhesion kinase 2 inhibitor	0.523	0.006
	Antiinflammatory	0.523	0.050
	Apoptosis antagonist	0.442	0.005
	Estrogen beta receptor agonist	0.298	0.004
	Antineoplastic (breast cancer)	0.297	0.056
	Autoimmune disorders treatment	0.334	0.086
	Estrogen antagonist	0.163	0.027
	Antineoplastic	0.281	0.164
	Antineoplastic (sarcoma)	0.184	0.077
	Epidermal growth factor receptor kinase inhibitor	0.145	0.044
	Antineoplastic (pancreatic cancer)	0.204	0.179
SPZ11	Transcription factor STAT3 inhibitor	0.833	0.003
	Transcription factor STAT inhibitor	0.825	0.003
	Transcription factor inhibitor	0.613	0.005
	Focal adhesion kinase 2 inhibitor	0.590	0.004
	Apoptosis antagonist	0.467	0.005
	Antiinflammatory	0.379	0.107
	Antineoplastic (brest cancer)	0.303	0.056
	Autoimmune disorders treatment	0.209	0.006
	Antineoplastic (bladder cancer)	0.185	0.064
	Antineoplastic (sarcoma)	0.184	0.076
	Epidermal growth factor receptor kinase inhibitor	0.138	0.049
	Tumour necrosis factor alpha antagonist	0.113	0.089
SPZ12	Transcription factor STAT3 inhibitor	0.611	0.006
	Transcription factor STAT inhibitor	0.578	0.009
	Autoimmune disorders treatment	0.486	0.032
	Focal adhesion kinase 2 inhibitor	0.421	0.022
	Antineoplastic (multiple myeloma)	0.376	0.031
	Transcription factor inhibitor	0.355	0.035
	Antiinflammatory	0.395	0.098
	Antineoplastic (breast cancer)	0.312	0.052
	Apoptosis antagonist	0.244	0.071
	I kappa B kinase 2 inhibitor	0.111	0.008

Discussion

All the synthesized compounds were docked by applying PDB (3ERT) along Human Estrogen Receptor Alpha Ligand-Binding Domain inhibitors taking Tamoxifen and Raloxifen as standard. Five analogs SPZ1,SPZ3, SPZ6, SPZ10 & SPZ11were showed very good mol-dock score pasturing in the middle -123.14 to -165.72 whereas both standard drugs Tamoxifen and Raloxifen showed mol-dock score -146.08 and -165.06 respectively which is comparatively lower then hypothetical synthesize compounds. Some hypothetical synthesized analogs were showed four number of H-bond interactions "i.e" (SPZ1, SPZ6 & SPZ11) both standard drugs H-bond interactions values 1 & 5. The Tamoxifen demonstrated H-bond interaction with amino acids O-Thr347 with bond length 3.41 Å while Raloxifen showed interaction with O-Glu353, O-Arg394, O-Gly521, O-His524 & O-Gly420 with bond length 3.14 Å, 2.87 Å, 3.31 Å, 3.17 Å and 3.20 Å. Numerous analogs were found to showed interaction with same amino acid O-Thr347, O-Glu353 & O-Arg394 and showed very acceptable bond length. The results are presented in Table 2. Pictures showing drug receptor interaction of standard and predicted compounds are labeled as Figure 3 to Figure 9.

Oral bioavailability is considered to be an essential feature for the development of effective pharmaceuticals. Swiss ADME online programme was utilised to determine the druglikeness features of the hybrids (SPZ1–SPZ12) of benzothiazole fused with 1,3,4-oxadiazole. Table 3 presents the findings. All of the developed derivatives' molecular weights were determined to be less than 500, which predicted their facile absorption, diffusion, and mobility. The log P (octanol-water partition coefficient) is a measure of molecular aquaphobicity. With the exception of SPZ2, SPZ4, SPZ7, SPZ8, SPZ9, and SPZ12 (Log P=5.05 to 5.99), all of the synthesised hits had Log P values of less than five, indicating strong membrane permeability of the compounds. In all of the anticipated hybrid counterparts, the numbers of hydrogen bond donors and acceptors were found to be fewer than five and ten, respectively. Topological polar surface area (TPSA), which was measured less than 160 A°, or in the range of 80.04 – 125.87 A°, is a very helpful statistic for forecasting the transport of drug molecules. Observation reveals that every anticipated derivative had favourable gastric absorption, signifying noteworthy oral bioavailability. Since all of these pharmacokinetic characteristics follow Lipinski's rule of five, all of the anticipated drugs have strong oral activity.

The LD50 of all the derivatives is more than that of the standard drug and was predicted to be in class IV. The compounds SPZ1, SPZ3, SPZ5, SPZ6, SPZ8, SPZ11, and SPZ12 were shown to have an active carcinogenicity, with a probability ranging from 0.51 to 0.68. The remaining derivatives, whose probabilities ranged from 0.52 to 0.74, were discovered to be inactive. It was discovered that SPZ1, SPZ3, SPZ6, and SPZ11 have an active mutagenicity with a probability of 0.51. It was discovered that every other chemical had an inactive possibility, ranging from 0.99 to 0.56. The immuno and cytotoxicity of the all the predicted derivatives was found to be inactive.

List of the specific biological activity and result of prediction with valid probability values- i.e. the values indicating possibility for a given activity type to be either observed (Pa) or not observed (Pi) was mentioned in Table 7 .Their values range 0.000 to 0.999. All the twelve hypothetical derivatives prediction data were compared with standard drug Tamoxifen and Raloxifen. The anticancer activitys were predicted through pass inlet. All the predicted compounds were showed transcription factor STAT3 and STAT inhibition potential, autoimmune disorders treatment, anti-inflammatory and anti-neoplatic activity. The compounds SPZ4, SPZ7, SPZ8, SPZ9, SPZ10, SPZ11, SPZ12 were showed anti-brest cancer activity.

Conclusion

In the present study, some benzothiazole base oxadiazole derivates from proposed scheme were predicted for their anti cancer activity by using PASS online software and ADMET study by using various Swiss ADME, ProTox II and molegro virtual docker 6.0 softwares. The results of the pharmacological screening indicated that benzothiazole based oxadiazoles possess significant anti-cancer activit. Among the predicted benzothiazole based oxadiazoles, compounds SPZ1, SPZ3, SPZ6, SPZ10 & SPZ11 emerged as lead compounds with good anti-cancer activity and good ADME and with minimum toxicity as compared with the reference drugs Tamoxifen and Raloxifen. Nevertheless, more synthesis of all the powerful compounds that have been predicted is required to determine the safety, effectiveness, and mechanism of this intriguing family of heterocyclic compounds.

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