World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 4
Page: 371-400

EXPLORING THE THERAPEUTIC POTENTIAL OF 2- AMINOBENZOTHIAZOLE DERIVATIVES IN CANCER TREATMENT: AN IN-SILICO APPROACH

Prof. Rachel Mathew[1], Vani V.[2], Ashni N.[3], Malavika A. M.*[4], Aravind V.[5]

[1]Professor, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy.

[2] Associate Professor, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy.

[3,4,5]Student, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy.

Article Received: 14 February 2026 | | ***Article Revised: 6 March 2026*** | | ***Article Accepted: 27 March 2026***

***Corresponding Author: Malavika A. M.**
Student, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy.
DOI: https://doi.org/10.5281/zenodo.19335788

How to cite this Article: Prof. Rachel Mathew, Vani V., Ashni N., Malavika A. M., Aravind V. (2026) EXPLORING THE THERAPEUTIC POTENTIAL OF 2- AMINOBENZOTHIAZOLE DERIVATIVES IN CANCER TREATMENT: AN IN-SILICO APPROACH. World Journal of Pharmaceutical Science and Research, 5(4), 371-400.

ABSTRACT

Cancer remains a major global health concern, highlighting the urgent need for effective and safer anticancer therapies. In the present study, 2-aminobenzothiazole derivatives were explored as potential anticancer agents using in-silico drug design approaches. Fifty derivatives were rationally designed and evaluated for their drug-likeness using Molinspiration, and all compounds satisfied Lipinski's Rule of Five, indicating favourable oral bioavailability. The predicted biological activity assessed through PASS suggested promising anticancer potential for the designed molecules. Molecular docking studies were carried out using AutoDock4 against the tyrosine kinase receptor (PDB ID: 1QCF) to understand ligand–protein interactions and estimate binding affinities. Several derivatives showed strong and stable binding within the active site of the target protein, highlighting the importance of structural modifications on anticancer activity. Overall, this in-silico study supports 2-aminobenzothiazole as a promising scaffold for the future development of novel anticancer agents and provides a strong basis for further experimental validation.

KEYWORDS: 2-Aminobenzothiazole, Anticancer Activity, Docking, In-silico design, Tyrosine Kinase, Benzothiazole.

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide and remains a major global health challenge. Cancer is characterized by the uncontrolled and aggressive proliferation of abnormal cells that invade and spread to distant organs and transforms into malignant tumours resulting in secondary disease. Cancer is among the four major non communicable disease making it one of the deadliest diseases in the world.[1,2]

Despite the major advances in cancer therapy, many anti-cancer agents have significant drawbacks. Therefore, there is a need to develop novel anticancer agents with improved safety and efficacy.

Drug discovery is a multifaceted process, which involves identification of a drug chemical therapeutically useful in treating and management of a disease condition. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy.[3]

The application of computational tools in drug discovery has become increasingly critical due to their efficiency in screening and evaluating large libraries of chemical compounds.[4]

Heterocycles are important pharmacophores and have significance to create privileged chemical structures possessing pharmacological activities. Benzothiazole derivatives exhibit remarkable and prevalent biological and pharmacological activities against different types of tumours and cancer cell lines.[5] It renders an extensive range of biological activities including anti-cancer, anti-bacterial, anti-tuberculosis, anti-diabetic, anthelmintic, anti-tumour, anti-viral, anti-oxidant, anti-inflammatory, anti-glutamate and anti-parkinsonism, anticonvulsant, muscle relaxant activities, neuroprotective, and inhibitors of several enzymes.[6]

Nitrogen/sulfur containing heterocycles are biologically important scaffolds, and they are widely present in a number of natural products and commercially available drugs.[1] 2-aminobenzothiazole stands as a prominently featured scaffold in medicinal chemistry, prevalent in bioactive molecules, particularly those pertaining to cancer agents. 2-aminobenzothiazole derivatives have emerged as novel antineoplastic agents, showcasing a diverse range of protein targets, including tyrosine kinases such as EGFR, CSF1R, VEGFR-2, MET, and FAK, serine/ threonine kinases such as Aurora, CK, CDK, DYRK2, and RAF, mutant p53protein, BCL-XL, PI3K kinase, HSP90, NSD1, HDAC, LSD1, DNA topoisomerases, FTO, mPGES-1, hCA IX/XII, SCD, and CXCR receptor.[7] Ongoing research continues to explore the potential applications and properties of benzothiazole compounds and their derivatives.[8]

The organic compound 2-aminobenzothiazole has the formula $C_7H_6N_2S$, and its structure can be expressed as a tautomerism of enamines. It is a heterocyclic aromatic amine that consists of a benzene ring fused to a thiazole group, which in turn is attached to an amino group. 2-Aminobenzothiazole's amino group gives it weakly basic properties.[9]

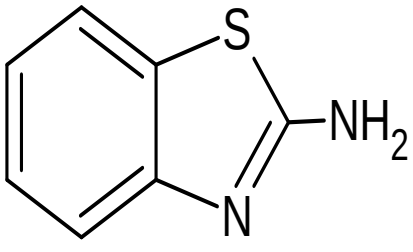


Figure 1: 2-ABT.

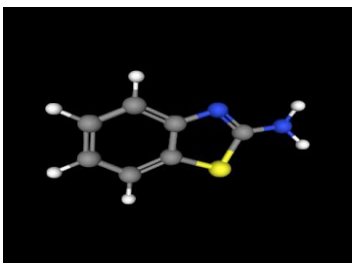


Figure 2: 3D Structure of 2-ABT.

The amino group of 2-aminobenzothiazole is an active and useful functionality, which could be tethered to many structural fragments or form various fused heterocycles. In addition, the 2-aminobenzothiazole core (exocyclic nitrogen, cyclic sulphur, and cyclic nitrogen) could provide suitable coordination site(s) for metals. Furthermore, 2-aminobenzothiazole acts as a bio isostere for aniline, 2-aminothiazole, 2-aminobenzimidazole, and other nitrogen- or oxygen-containing heterocycles. At the structural level, the 2-aminobenzothiazole fragment can be involved in formation of hydrogen bonds (as a hydrogen bond acceptor and/or donor), chalcogen bonds, as well as π-π stacking/van der Waals contacts with the specific amino acid residues on target proteins, which contribute to inhibitory activity.[10]

Therefore, the present study focuses on the design and in-silico evaluation of 2-aminobenzothiazole derivatives as potential anticancer agents using computational drug discovery approaches.

MATERIALS AND METHODS

1. DESIGN OF LIGANDS

A series of fifty derivatives of 2-aminobenzothiazole were designed and chemical structures were drawn using chemical drawing software ACD/ChemSketch and molecular optimization was performed to obtain stable conformations suitable for computational analysis.

2. DRUG LIKENESS AND PHYSIOCHEMICAL PROPERTY ANALYSIS

The physicochemical and drug likeness of the compounds were calculated by using cheminformatics tool Molinspiration. This software calculates important molecular descriptors that help predict whether a compound possesses characteristics suitable for drug development. Key parameters such as molecular weight (MW), lipophilicity (LogP), number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), and topological polar surface area (TPSA) were determined for all designed compounds. These parameters were analysed according to Lipinski's Rule of Five, which is widely used to evaluate the oral bioavailability of potential drug candidates.

According to Lipinski's rule, a compound is considered to have favourable drug-like properties if it satisfies the following criteria: molecular weight less than 500 g/mol, LogP value below 5, hydrogen bond donors not exceeding 5, and hydrogen bond acceptors not exceeding 10. Compounds meeting these criteria are more likely to exhibit good absorption and permeability.[11]

3. PASS ACTIVITY PREDICTION

The biological activity of the designed compounds was predicted using the online tool PASS Online available through the Way2Drug PASS Online server. PASS (Prediction of Activity Spectra for Substances) estimates possible biological activities of chemical compounds based on their structural features.

The chemical structures of all fifty compounds were submitted to the server, and the probability of activity (Pa) and probability of inactivity (Pi) values were generated. A compound is considered to have potential biological activity when Pa is greater than Pi. In the present study, PASS prediction was performed to evaluate the potential proto-oncogene tyrosine-protein kinase Fgr inhibitory activity of the designed compounds.[12]

4. MOLECULAR DOCKING STUDY

A total of fifty 2-aminobenzothiazole conjugates were selected from various literature sources and molecular libraries using SwissSimilarity for computational docking studies. These compounds were selected based on their structural diversity and reported biological relevance.

The three-dimensional crystal structure of protein tyrosine kinase (PDB ID: 1QCF, co-crystallized with inhibitor PP1) was retrieved from the Protein Data Bank at a resolution of 2.55 Å. The protein structure was pre-processed using ChimeraX software by removing unwanted residues and water molecules, followed by the addition of hydrogen atoms to stabilize the protein structure and prepare it for docking studies.

The ligands were selected from molecular libraries through virtual screening using Swiss Similarity and from various literature reports. The 2D structures of the ligands were downloaded from the PubChem database in .sdf format and converted into their 3D structures using NovoPro.[14,15,16]

Ligand preprocessing was performed using Avogadro software by adding hydrogen atoms, optimizing molecular geometry, and performing energy minimization in order to obtain stable conformations suitable for docking analysis.[19]

Docking Procedure

Molecular docking studies were carried out using AutoDock4 to evaluate the binding affinity and interaction pattern between the prepared ligands and the active site of the target protein. The prepared protein and optimized ligand structures were converted into the appropriate file formats required for docking analysis.

Prior to docking, grid maps were generated to define the active binding region of the protein. The grid box was centered on the active site to allow the ligand molecules to explore the binding pocket effectively. Docking calculations were performed using the Lamarckian Genetic Algorithm, which is implemented in AutoDock for predicting optimal ligand conformations and binding orientations.

For each ligand, multiple docking runs were performed to obtain the most stable binding pose. The docked complexes were ranked based on their binding energy values (kcal/mol), and the lowest-energy conformation was selected as the most favourable binding pose.[17,20]

Ligand–Protein Interaction Analysis

The interaction between the docked ligands and the target protein was analysed using BIOVIA Discovery Studio. The ligand–protein complexes obtained after docking were imported into the software to visualize and analyse the binding interactions. Two-dimensional (2D) interaction diagrams were generated to identify important interactions between the ligands and amino acid residues present in the active site of the protein. Key interactions such as hydrogen bonding, hydrophobic interactions, π–π stacking, and van der Waals interactions were examined to understand the stability of the ligand–protein complexes.[18]

5. ADMET PREDICTION

The pharmacokinetic and toxicity properties of the designed compounds were predicted using the online platform ADMETlab 3.0. ADMET analysis is widely used in drug discovery to evaluate Absorption, Distribution, Metabolism, Excretion, and Toxicity properties of potential drug candidates.

The chemical structures of the designed 2-aminobenzothiazole derivatives were submitted to the ADMETlab 3.0 server in SMILES format to predict their pharmacokinetic and toxicity profiles. Various parameters including human intestinal absorption, blood–brain barrier permeability, plasma protein binding, cytochrome P450 interactions, clearance, and toxicity endpoints were analysed.

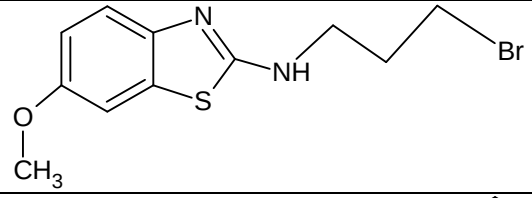
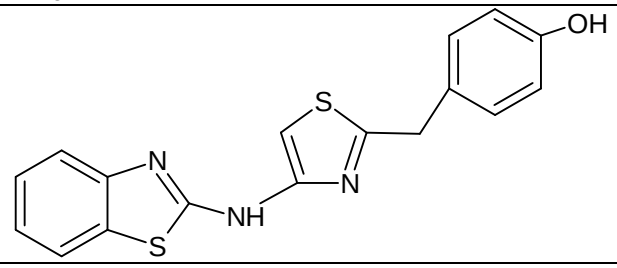
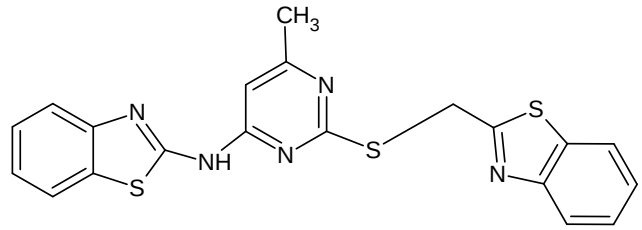
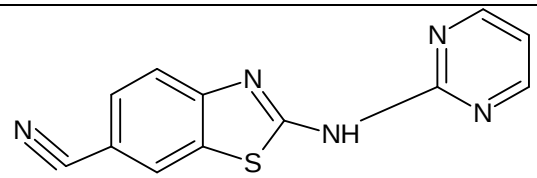
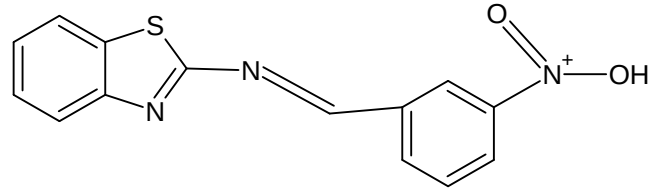
These predictions help to assess whether the compounds possess suitable drug-like properties and safety profiles, which are essential for further development as therapeutic agents.[13]

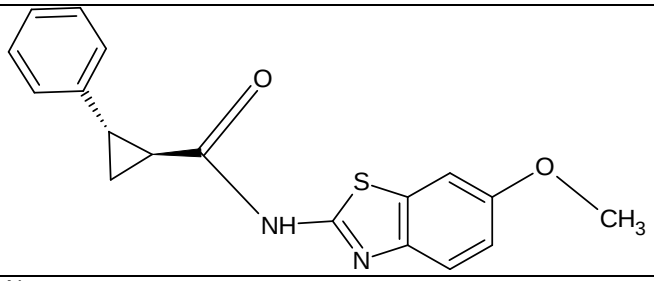
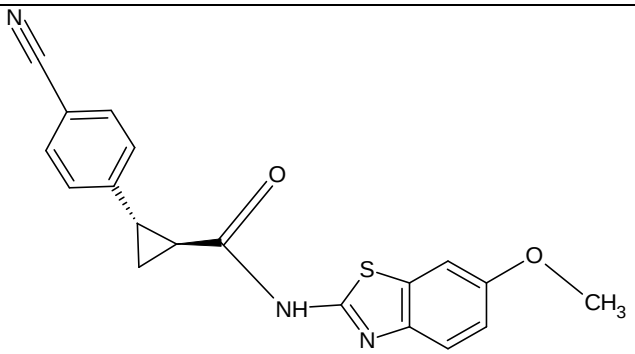
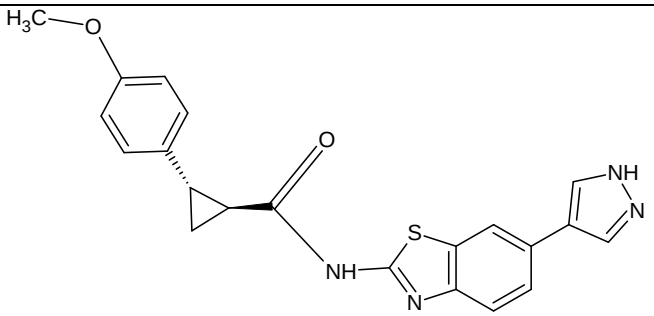
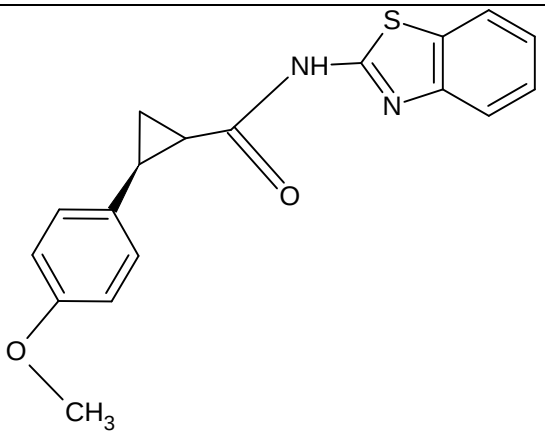
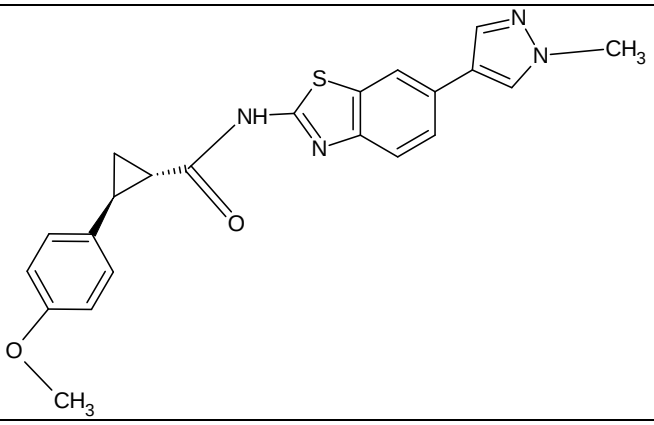
RESULTS AND DISCUSSION

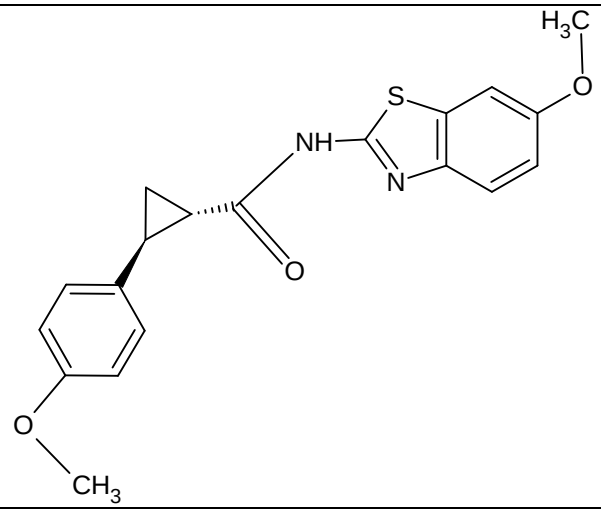
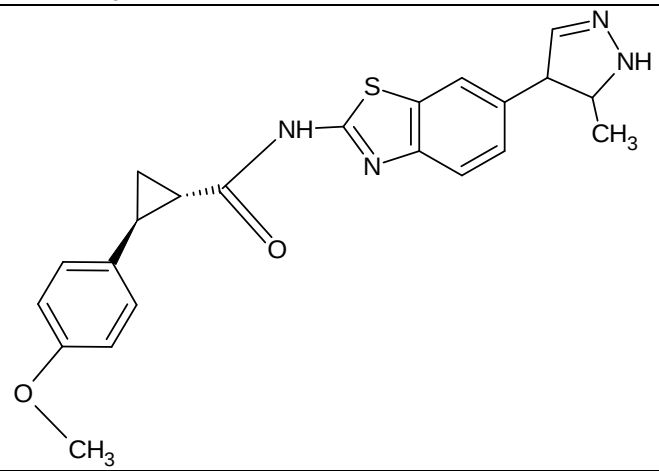
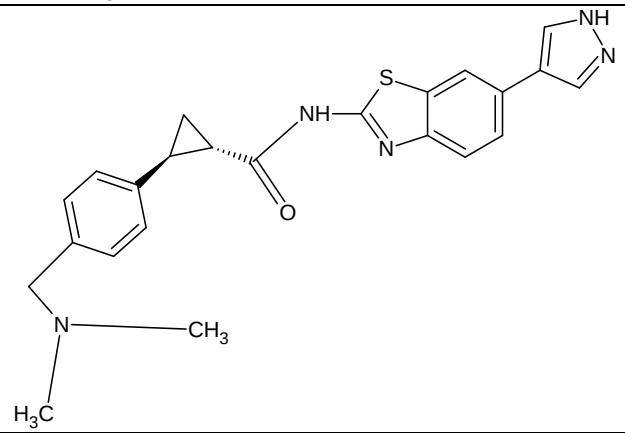
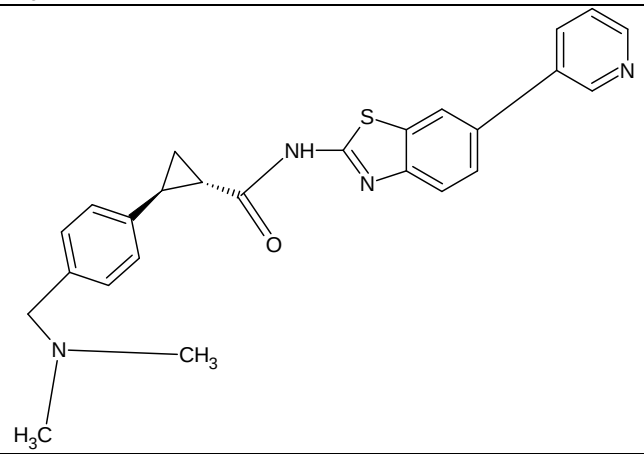
1. COMPOUND STRUCTURE AND SMILES

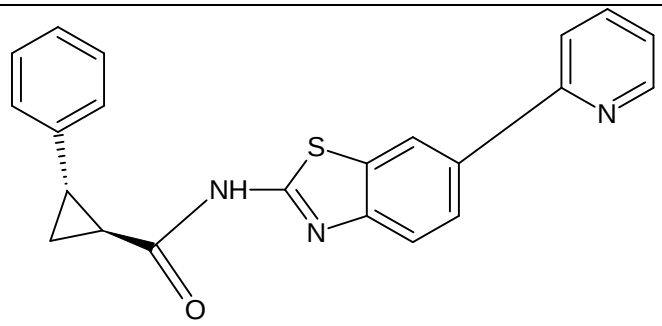
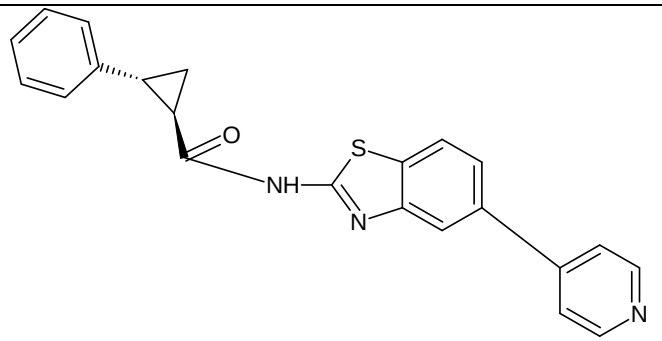
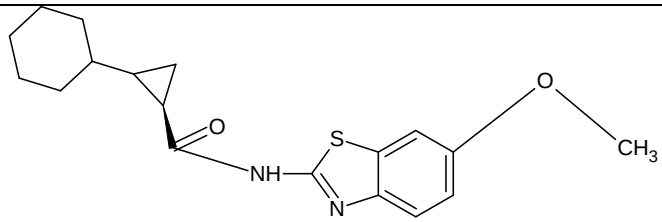
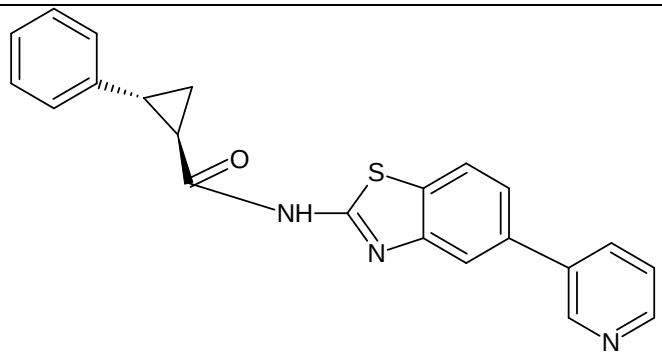
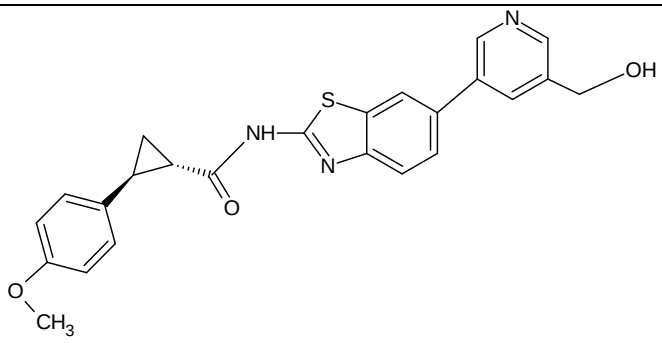
By using ACD/Chemsketch the 2D structures of proposed 2-aminobenzothiazole derivatives having anticancer activity were drawn.

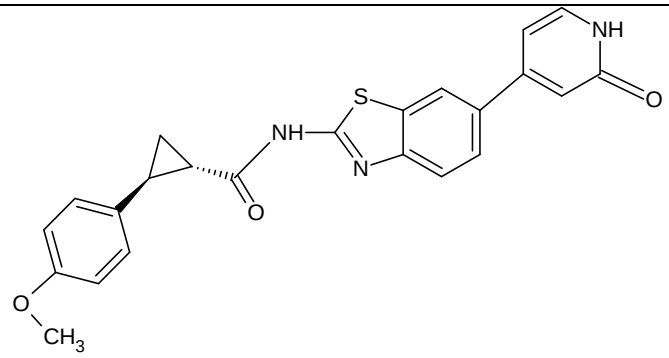
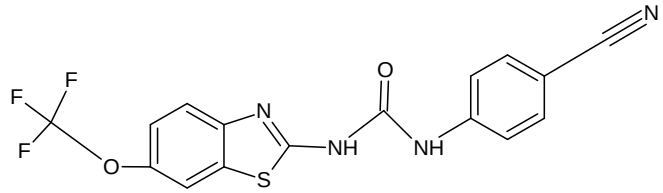
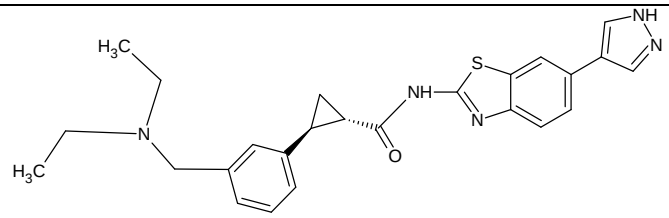
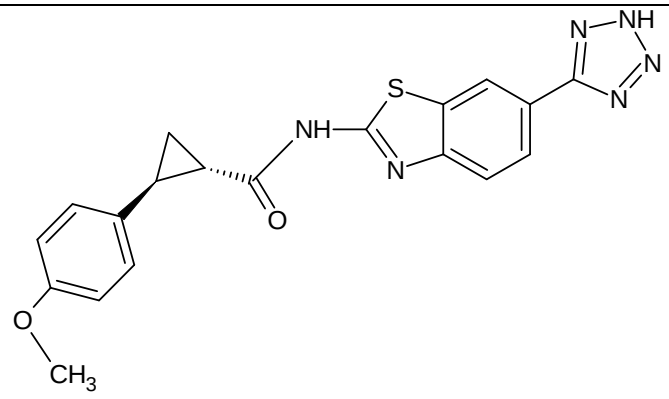
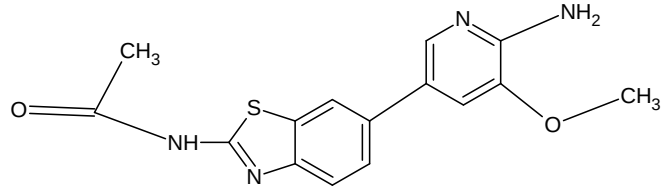
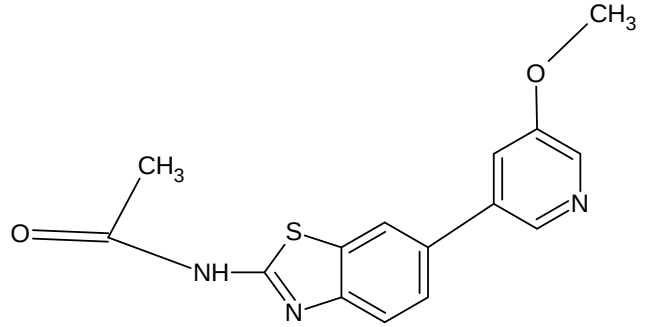
Table 1: Table Showing Structures of 2-ABT Derivatives Along With their IUPAC Names and SMILES Notation.

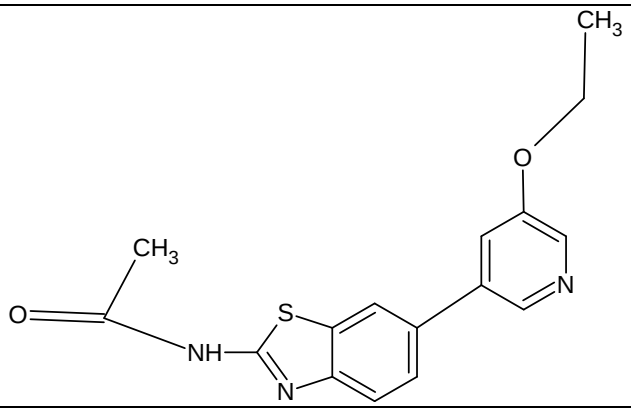
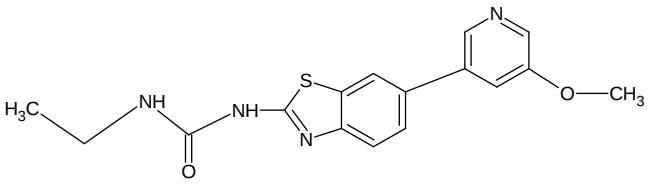
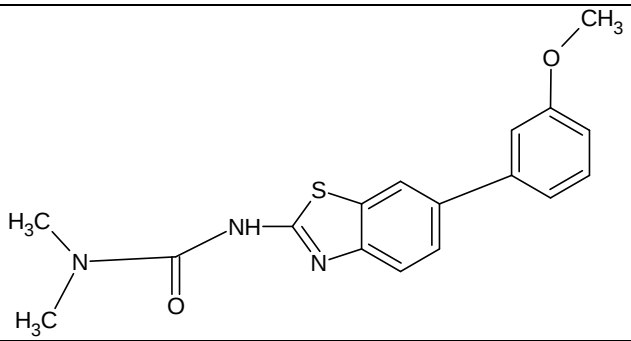
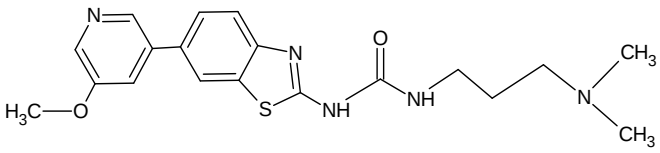
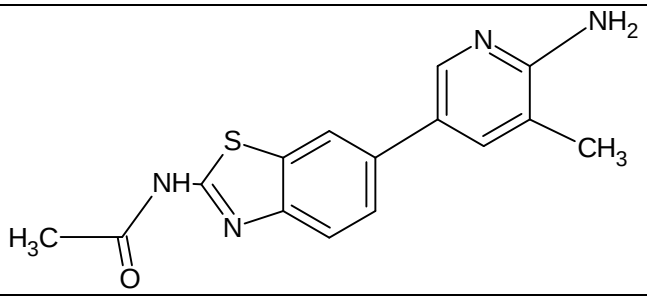
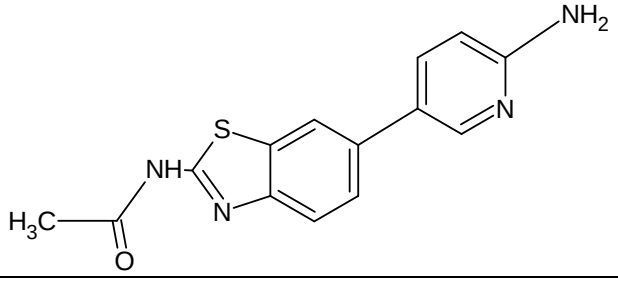
COMPOUND CODE	STRUCTURE	SMILES NOTATION	IUPAC NAME
B1		BrCCCNc1sc2cc(ccc2n1)OC	*N*-(3-bromopropyl)-6-methoxy-1,3-benzothiazol-2-amine
B2		Oc1ccc(Cc2scc(Nc3sc4ccccc4n3)n2)cc1	4-({4-[(1,3-benzothiazol-2-yl)amino]-1,3-thiazol-2-yl}methyl)phenol
B3		Cc1nc(SCc2sc3ccccc3n2)nc(Nc2sc3ccccc3n2)c1	*N*-[2-(1,3-benzothiazol-2-ylmethylsulfanyl)-6-methylpyrimidin-4-yl]-1,3-benzothiazol-2-amine
B4		N#Cc1cc2sc(Nc3ncccn3)nc2cc1	2-[(pyrimidin-2-yl)amino]-1,3-benzothiazole-6-carbonitrile
B5		O[N+](=O)c1cc(\C=N\c2sc3ccccc3n2)ccc1	(3-{(*E*)-[(1,3-benzothiazol-2-yl)imino]methyl}phenyl)(hydroxy)(oxo)ammonium

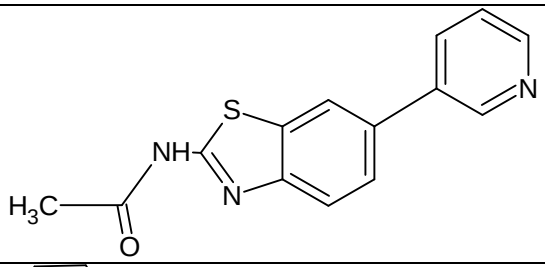
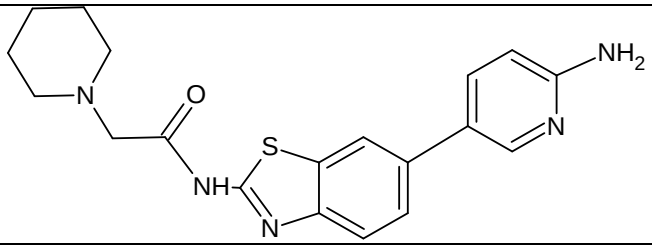
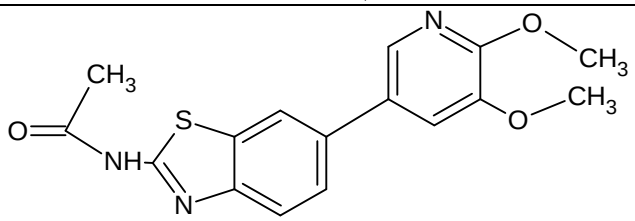
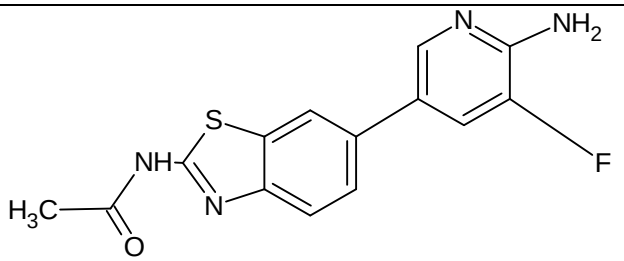
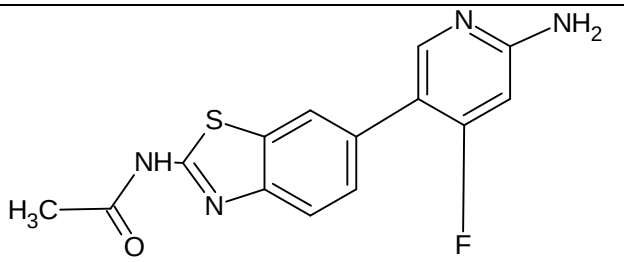
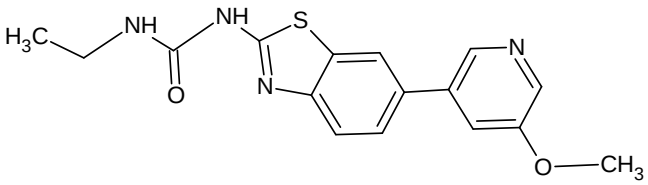
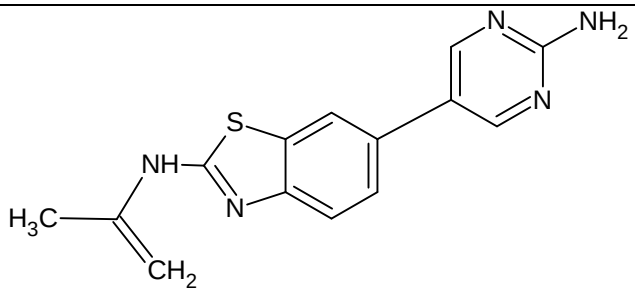
B6		O=C(Nc1sc2cc(ccc2n1)OC)[C@H]1C[C@@H]1c1ccccc1	(1*S*,2*S*)-*N*-(6-methoxy-1,3-benzothiazol-2-yl)-2-phenylcyclopropane-1-carboxamide
B7		O=C(Nc1sc2cc(ccc2n1)OC)[C@H]1C[C@@H]1c1ccc(cc1)C#N	(1*S*,2*S*)-2-(4-cyanophenyl)-*N*-(6-methoxy-1,3-benzothiazol-2-yl)cyclopropane-1-carboxamide
B8		O=C(Nc1sc2cc(ccc2n1)c1cn[NH]c1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-2-(4-methoxyphenyl)-*N*-[6-(1*H*-pyrazol-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B9		O=C(Nc1sc2ccccc2n1)C1C[C@@H]1c1ccc(cc1)OC	(2*S*)-*N*-(1,3-benzothiazol-2-yl)-2-(4-methoxyphenyl)cyclopropane-1-carboxamide
B10		O=C(Nc1sc2cc(ccc2n1)c1cn(C)nc1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-2-(4-methoxyphenyl)-*N*-[6-(1-methylpyrazol-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide

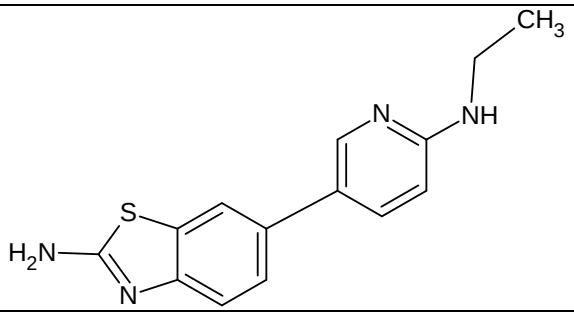
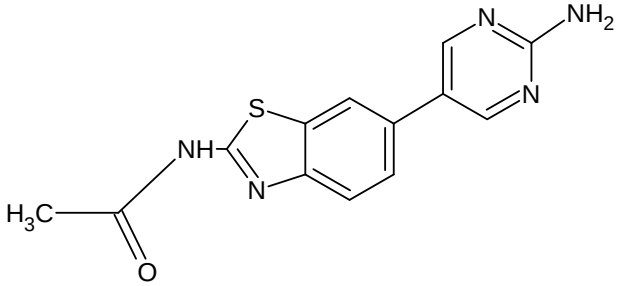
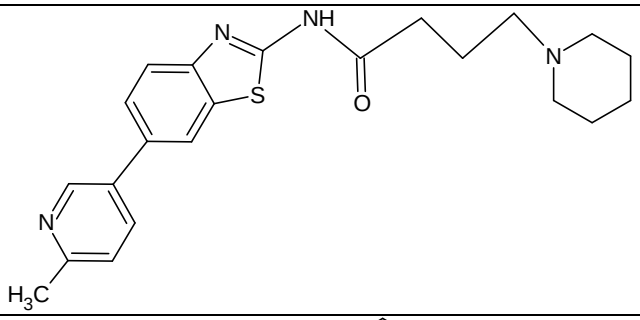
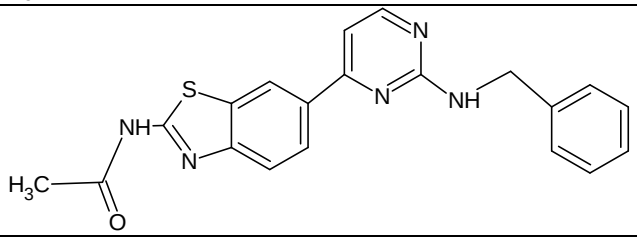
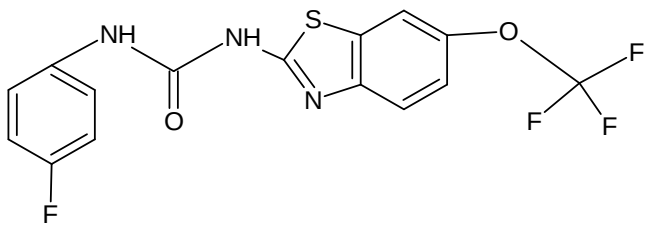
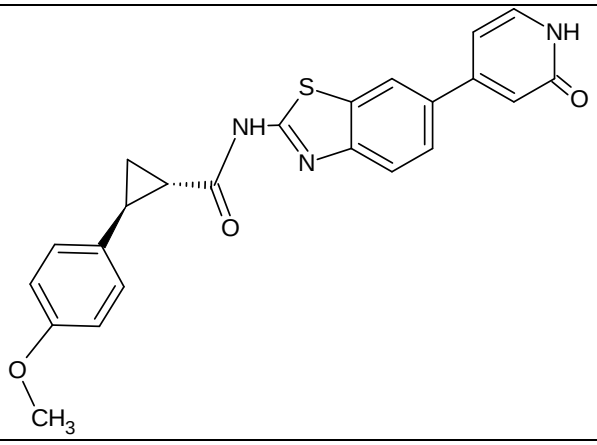
B11		O=C(Nc1sc2cc(ccc2n1)OC)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-*N*-(6-methoxy-1,3-benzothiazol-2-yl)-2-(4-methoxyphenyl) cyclopropane-1-carboxamide
B12		O=C(Nc1sc2cc(ccc2n1)C1C=NNC1C)[C@H]1C[C@@H]1c1ccc(cc1)OC	
B13		O=C(Nc1sc2cc(ccc2n1)c1cn[NH]c1)[C@H]1C[C@@H]1c1ccc(cc1)CN(C)C	(1*S*,2*S*)-2-[4-[(dimethylamino)methyl]phenyl]-*N*-[6-(1*H*-pyrazol-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B14		O=C(Nc1sc2cc(ccc2n1)c1cccnc1)[C@H]1C[C@@H]1c1ccc(cc1)CN(C)C	(1*S*,2*S*)-2-[4-[(dimethylamino)methyl]phenyl]-*N*-(6-pyridin-3-yl-1,3-benzothiazol-2-yl)cyclopropane-1-carboxamide

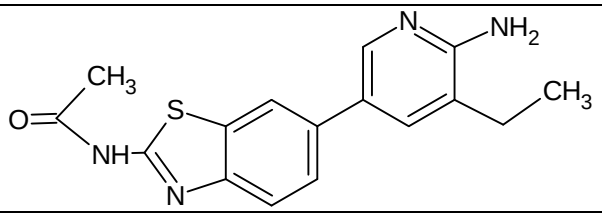
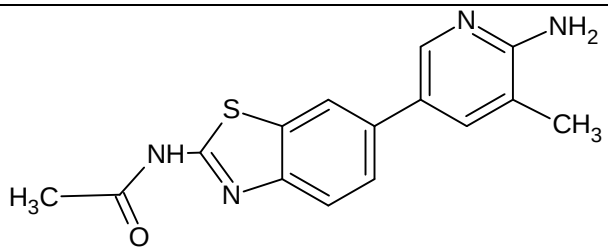
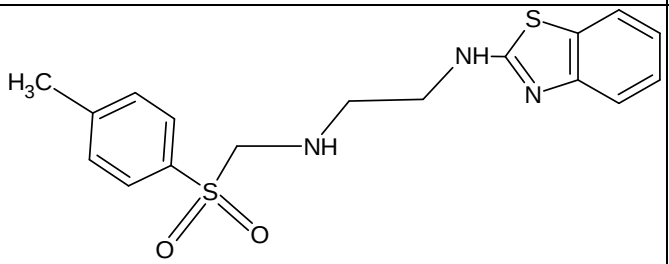
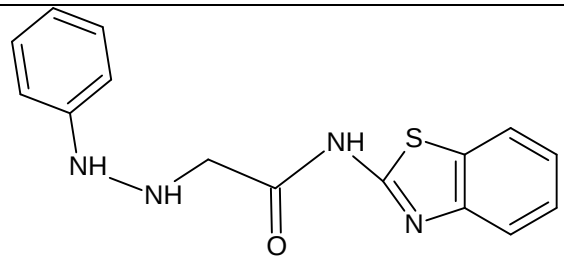
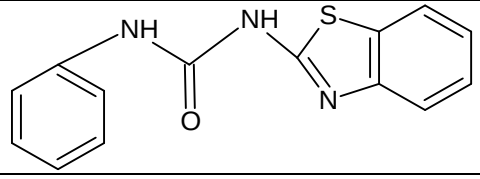
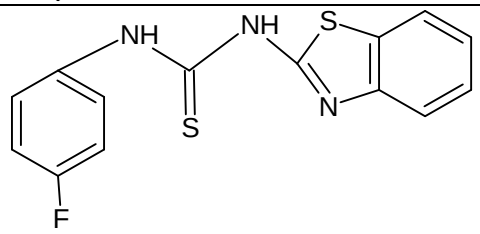
B15		O=C(Nc1sc2cc(ccc2n1)c1ccccn1)[C@H]1C[C@@H]1c1ccccc1	(1*S*,2*S*)-2-phenyl-*N*-[6-(pyridin-2-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B16		O=C(Nc1sc2ccc(cc2n1)c1ccncc1)[C@@H]1C[C@H]1c1ccccc1	(1*R*,2*R*)-2-phenyl-*N*-[5-(pyridin-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B17		O=C(Nc1sc2cc(ccc2n1)OC)[C@@H]1CC1C1CCCCC1	(1*R*)-2-cyclohexyl-*N*-(6-methoxy-1,3-benzothiazol-2-yl)cyclopropane-1-carboxamide
B18		O=C(Nc1sc2ccc(cc2n1)c1cccnc1)[C@@H]1C[C@H]1c1ccccc1	(1*R*,2*R*)-2-phenyl-*N*-[5-(pyridin-3-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B19		O=C(Nc1sc2cc(ccc2n1)c1cc(CO)cnc1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-*N*-[6-[5-(hydroxymethyl)-3-pyridinyl]-1,3-benzothiazol-2-yl]-2-(4-methoxyphenyl)cyclopropane-1-carboxamide

B20		O=C(Nc1sc2cc(ccc2n1)C=1C=CNC(=O)C=1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-2-(4-methoxyphenyl)-*N*-[6-(2-oxo-1*H*-pyridin-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B21		O=C(Nc1sc2cc(ccc2n1)OC(F)(F)F)Nc1ccc(C#N)cc1	*N*-(4-cyanophenyl)-*N*'-[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]urea
B22		O=C(Nc1sc2cc(ccc2n1)c1cn[NH]c1)[C@H]1C[C@@H]1c1cccc(CN(CC)CC)c1	
B23		O=C(Nc1sc2cc(ccc2n1)c1nn[NH]n1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-2-(4-methoxyphenyl)-*N*-[6-(2*H*-tetrazol-5-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide
B24		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)c(c1)OC	*N*-[6-(6-amino-5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B25		COc1cncc(c1)c1cc2sc(nc2cc1)NC(=O)C	*N*-[6-(5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide

B26		O=C(C)Nc1sc2cc(ccc2n1)c1cncc(c1)OCC	*N*-[6-(5-ethoxypyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B27		O=C(Nc1sc2cc(ccc2n1)c1cncc(c1)OC)NCC	*N*-ethyl-*N*'-[6-(5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]urea
B28		COc1cc(ccc1)c1ccc2nc(sc2c1)NC(=O)N(C)C	*N*'-[6-(3-methoxyphenyl)-1,3-benzothiazol-2-yl]-*N*,*N*-dimethylurea
B29		COc1cc(cnc1)c1ccc2nc(sc2c1)NC(=O)NCCCN(C)C	*N*-[3-(dimethylamino)propyl]-*N*'-[6-(5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]urea
B30		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)c(C)c1	*N*-[6-(6-amino-5-methylpyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B31		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)cc1	*N*-[6-(6-aminopyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide

B32		O=C(C)Nc1sc2cc(ccc2n1)c1cnccc1	*N*-[6-(pyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B33		O=C(Nc1sc2cc(ccc2n1)c1ccc(N)nc1)CN1CCCCC1	*N*-[6-(6-aminopyridin-3-yl)-1,3-benzothiazol-2-yl]-2-(piperidin-1-yl)acetamide
B34		COc1ncc(cc1OC)c1cc2sc(nc2cc1)NC(=O)C	*N*-[6-(5,6-dimethoxypyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B35		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)c(F)c1	*N*-[6-(6-amino-5-fluoropyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide—fluorine (1/1)
B36		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)cc1F	*N*-[6-(6-amino-4-fluoropyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B37		O=C(Nc1sc2cc(ccc2n1)c1cncc(c1)OC)NCC	*N*-ethyl-*N*'-[6-(5-methoxypyridin-3-yl)-1,3-benzothiazol-2-yl]urea
B38		CC(=C)Nc1sc2cc(ccc2n1)c1cnc(N)nc1	6-(2-aminopyrimidin-5-yl)-*N*-(prop-1-en-2-yl)-1,3-benzothiazol-2-amine—water (1/1)

B39		Nc1sc2cc(ccc2n1)c1cnc(cc1)NCC	6-[6-(ethylamino)pyridin-3-yl]-1,3-benzothiazol-2-amine
B40		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)nc1	*N*-[6-(2-aminopyrimidin-5-yl)-1,3-benzothiazol-2-yl]acetamide
B41		O=C(CCCN1CCCCC1)Nc1sc2cc(ccc2n1)c1ccc(C)nc1	
B42		O=C(C)Nc1sc2cc(ccc2n1)c1ccnc(n1)NCc1ccccc1	*N*-{6-[2-(benzylamino)pyrimidin-4-yl]-1,3-benzothiazol-2-yl}acetamide
B43		O=C(Nc1sc2cc(ccc2n1)OC(F)(F)F)Nc1ccc(F)cc1	*N*-(4-fluorophenyl)-*N*'-[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]urea
B44		O=C(Nc1sc2cc(ccc2n1)C=1C=CNC(=O)C=1)[C@H]1C[C@@H]1c1ccc(cc1)OC	(1*S*,2*S*)-2-(4-methoxyphenyl)-*N*-[6-(2-oxo-1*H*-pyridin-4-yl)-1,3-benzothiazol-2-yl]cyclopropane-1-carboxamide

B45		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)c(c1)CC	*N*-[6-(6-amino-5-ethylpyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B46		O=C(C)Nc1sc2cc(ccc2n1)c1cnc(N)c(C)c1	*N*-[6-(6-amino-5-methylpyridin-3-yl)-1,3-benzothiazol-2-yl]acetamide
B47		O=S(=O)(CNCCNc1sc2ccccc2n1)c1ccc(C)cc1	N^1-(1,3-benzothiazol-2-yl)-N^2-[(4-methylbenzene-1-sulfonyl)methyl]ethane-1,2-diamine
B48		O=C(Nc1sc2ccccc2n1)CNNc1ccccc1	*N*-(1,3-benzothiazol-2-yl)-2-(2-phenylhydrazin-1-yl)acetamide
B49		O=C(Nc1sc2ccccc2n1)Nc1ccccc1	*N*-(1,3-benzothiazol-2-yl)-*N*'-phenylurea
B50		S=C(Nc1sc2ccccc2n1)Nc1ccc(F)cc1	*N*-(1,3-benzothiazol-2-yl)-*N*'-(4-fluorophenyl)thiourea

2. MOLINSPIRATION ANALYSIS

Fifty analogues of 2-Aminobenzothiazole were designed. Initially the designed analogues were subjected to rule analysis using Molinspiration software. These compounds did not show any violations from the Lipinski rule of five. The results of Molinspiration of 50 derivatives are shown in the table.

Table no 2: Molinspiration values of Proposed Derivatives.

Compound code	Log p	Mol.wt	nHAcc	nHDon	Nrotb	nviolation
B1	2.83	303.23	3	2	5	0
B2	3.733	341.46	4	3	4	0
B3	4.36	423.59	5	2	5	0
B4	1.81	255.31	5	2	2	0

B5	3.96	283.31	5	0	3	0
B6	3.71	357.48	5	2	4	0
B7	3.67	349.42	5	1	4	0
B8	3.53	398.53	6	3	5	0
B9	3.50	332.47	4	2	4	0
B10	3.53	398.53	6	3	5	0
B11	3.50	332.47	4	2	4	0
B12	3.65	412.56	6	2	5	0
B13	3.20	419.55	6	3	6	0
B14	3.82	430.58	5	2	6	0
B15	3.94	373.48	4	2	4	0
B16	3.80	373.48	4	2	4	0
B17	4.53	332.47	4	2	3	0
B18	4.02	73.48	4	2	4	0
B19	3.48	433.53	6	3	6	0
B20	3.52	419.51	6	3	5	0
B21	4.02	405.40	5	2	5	0
B22	3.95	447.61	6	3	8	0
B23	2.78	394.46	8	3	5	0
B24	3.96	283.31	5	0	3	0
B25	2.62	299.36	5	1	3	0
B26	2.99	313.38	5	1	4	0
B27	3.28	328.40	6	2	4	0
B28	3.66	327.41	5	1	3	0
B29	3.21	385.49	7	2	7	0
B30	2.62	298.37	5	3	2	0
B31	2.24	284.34	5	3	2	0
B32	2.41	269.33	4	1	2	0
B33	3.50	367.48	6	3	4	0
B34	4.56	327.41	5	1	5	0
B35	2.33	302.33	5	3	2	0
B36	2.33	302.33	5	3	2	0
B37	3.28	328.40	6	2	4	0
B38	3.28	283.36	5	3	3	0
B39	3.25	270.36	4	3	3	0
B40	1.51	285.33	6	3	2	0
B41	3.91	394.54	5	1	6	0
B42	4.95	331.45	4	3	2	0
B43	4.79	371.31	5	2	4	0
B44	4.46	431.52	6	2	6	0
B45	2.28	314.41	5	3	3	0
B46	2.28	314.41	5	3	3	0
B47	3.07	361.49	5	2	7	0
B48	3.28	298.37	5	3	5	0
B49	3.70	269.33	4	2	2	0
B50	3.74	283.21	5	3	5	0

The Molinspiration evaluation of the 2-aminobenzothiazole derivatives shows that all compounds comply with Lipinski's Rule of Five, with no violations observed. The physicochemical parameters, including log P, molecular weight, hydrogen bond donors and acceptors, and rotatable bonds, are within acceptable limits for most compounds.

The log P values indicate a suitable balance between hydrophilicity and lipophilicity, while the molecular weights remain within the desirable range for drug-like molecules. Hydrogen bonding capacity and molecular flexibility are also found to be appropriate, supporting potential interactions with biological targets.

Overall, the results suggest that the designed compounds possess favorable drug-like characteristics and may be considered suitable for further studies such as docking and ADMET evaluation.

3. PASS PREDICTION

Table no 3: PASS (Prediction of Activity Spectra for Substances) Values of Proposed Derivatives.

COMPOUND CODE	Pa	Pi
B1	0.514	0.004
B2	0.513	0.004
B3	0.579	0.003
B4	0.625	0.002
B5	0.505	0.004
B6	0.574	0.003
B7	0.556	0.003
B8	0.513	0.004
B9	0.574	0.003
B10	0.513	0.004
B11	0.578	0.003
B12	0.524	0.004
B13	0.518	0.004
B14	0.544	0.003
B15	0.587	0.003
B16	0.573	0.003
B17	0.572	0.003
B18	0.560	0.003
B19	0.510	0.004
B20	0.524	0.004
B21	0.577	0.003
B22	0.475	0.005
B23	0.505	0.004
B24	0.493	0.004
B25	0.519	0.004
B26	0.502	0.004
B27	0.581	0.003
B28	0.601	0.003
B29	0.578	0.003
B30	0.503	0.004
B31	0.521	0.004
B32	0.533	0.004
B33	0.490	0.005
B34	0.510	0.004
B35	0.491	0.005
B36	0.499	0.004
B37	0.581	0.003
B38	0.535	0.004
B39	0.503	0.004
B40	0.537	0.004
B41	0.484	0.005
B42	0.506	0.004
B43	0.586	0.003
B44	0.524	0.004
B45	0.476	0.005
B46	0.503	0.004
B47	0.487	0.005
B48	0.533	0.004
B49	0.697	0.002
B50	0.554	0.003

The PASS prediction results for the 2-aminobenzothiazole derivatives indicate that most compounds exhibit moderate to good biological activity, as reflected by their Pa values ranging from 0.475 to 0.697, which are consistently higher than the corresponding Pi values.

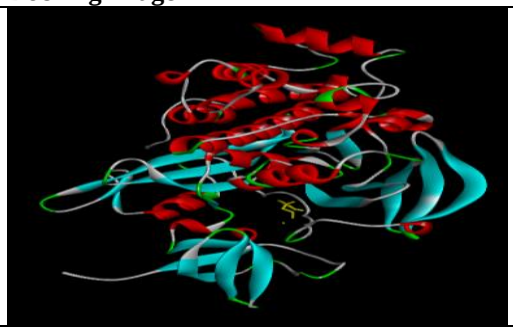
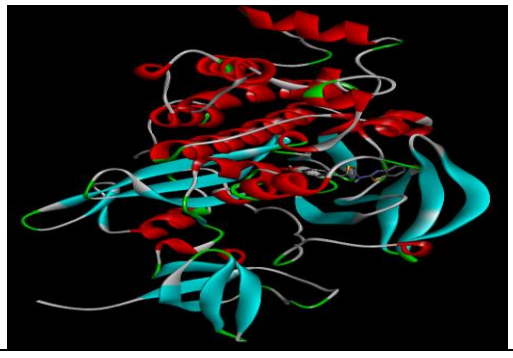
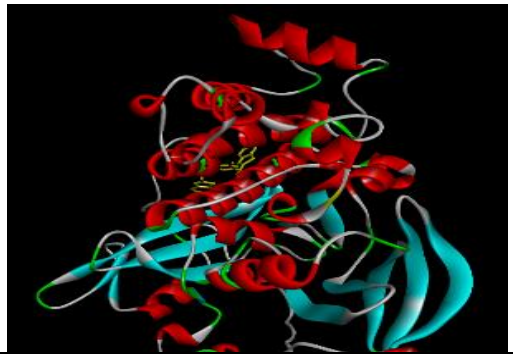
All compounds show Pa > Pi, suggesting a higher probability of exhibiting the predicted biological activity. Notably, compounds such as B4, B28, B27, B37, and B49 demonstrate relatively higher Pa values, indicating stronger predicted activity compared to others in the series.

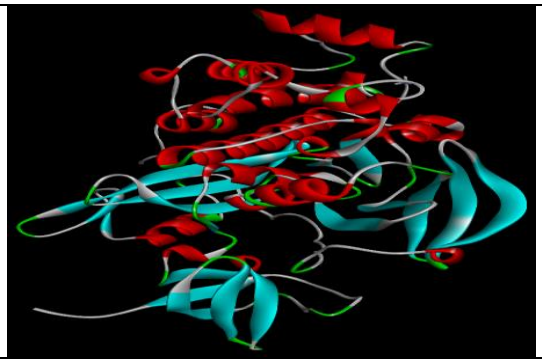
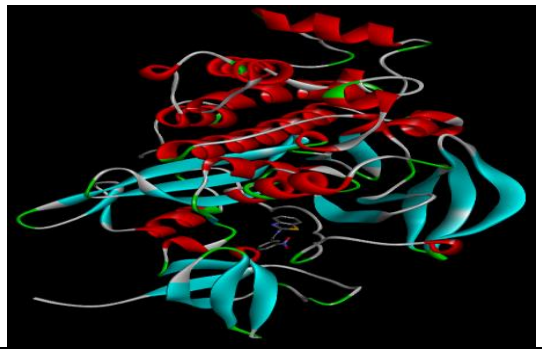
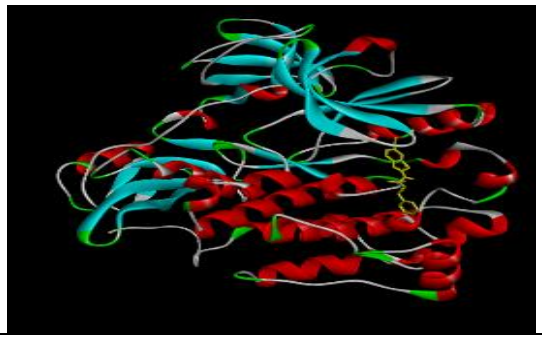
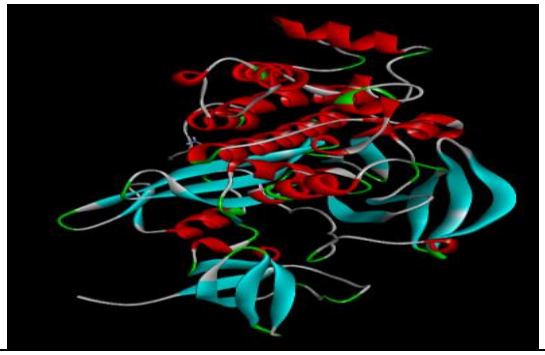
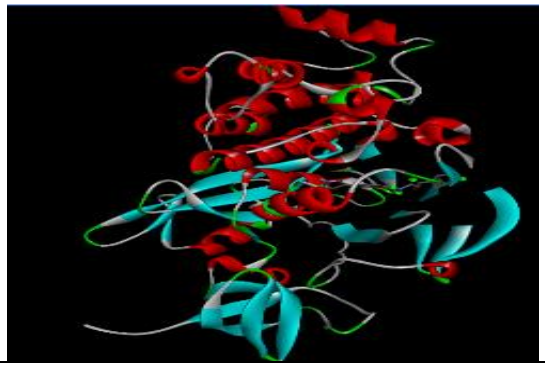
Overall, the PASS analysis supports the potential biological relevance of the designed compounds and highlights several promising candidates for further validation through molecular docking and experimental studies.

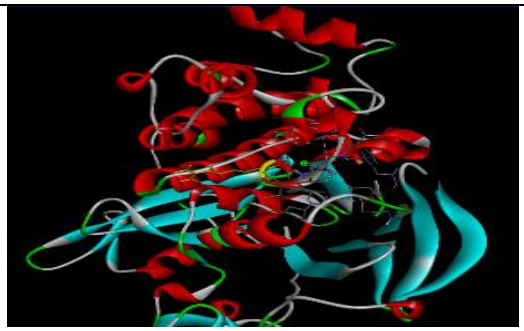
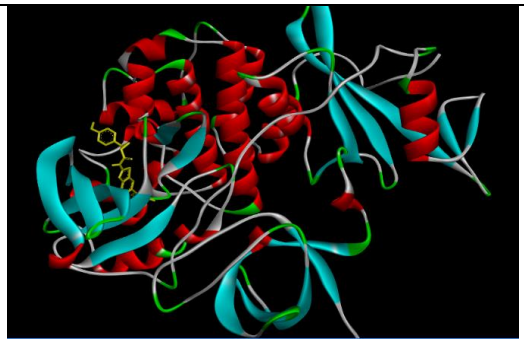
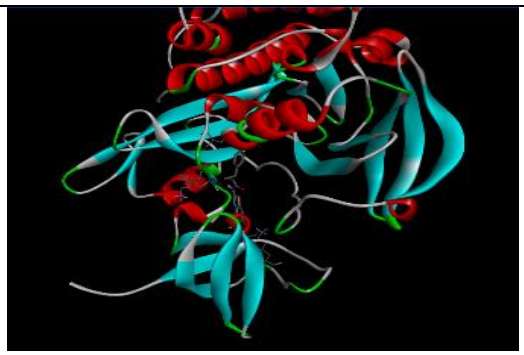
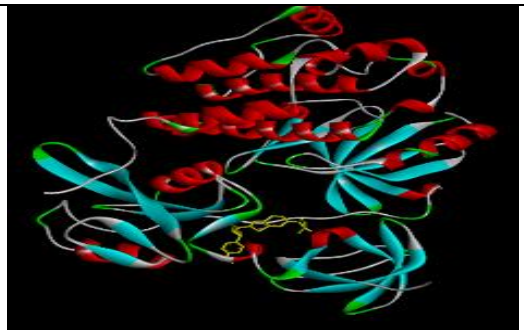
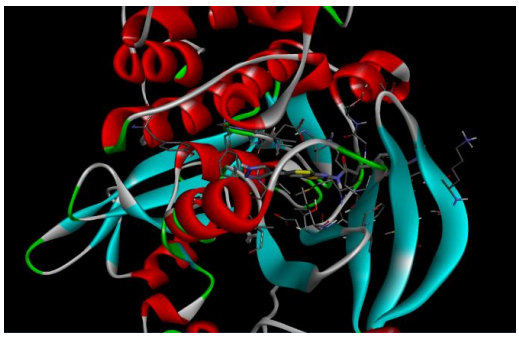
4. MOLECULAR DOCKING STUDIES

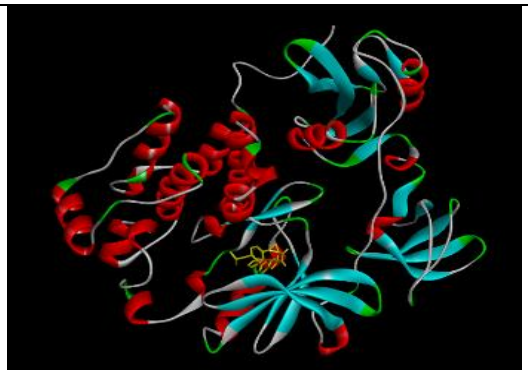
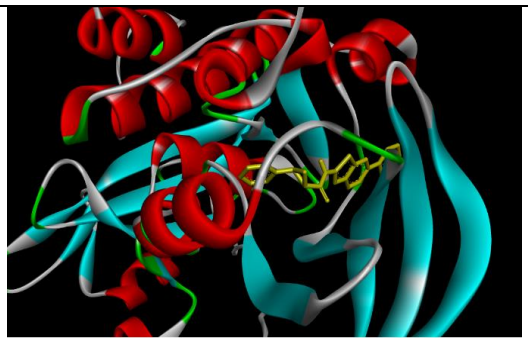
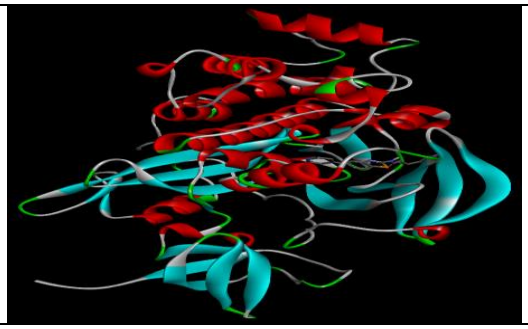
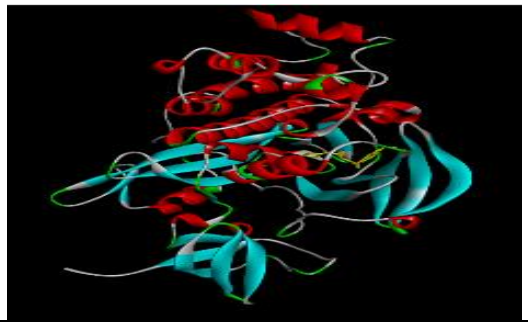
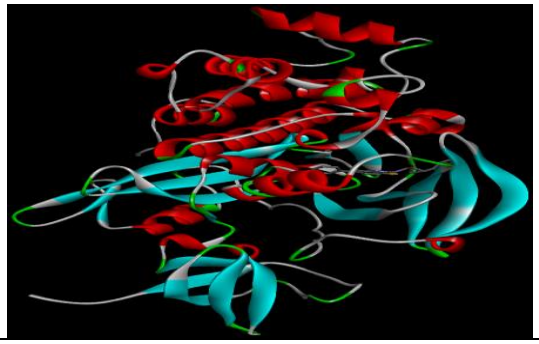
The fifty analogues were subjected to docking studies against Tyrosine Kinase receptor (PDB ID: 1QCF) to evaluate their anticancer activity. The docking simulations was carried out in AutoDock. The docking scores along with the corresponding ligand–protein complexes are presented in Table 6.

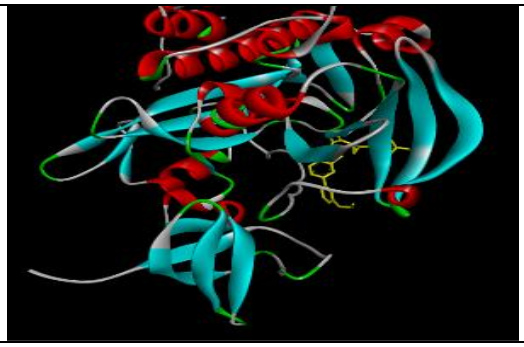
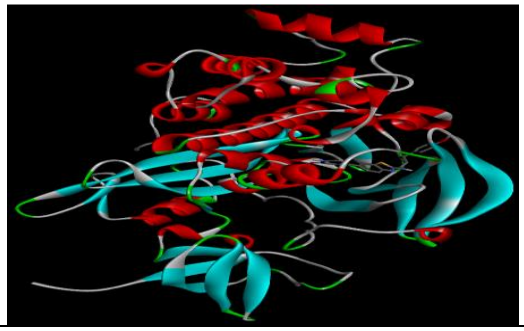
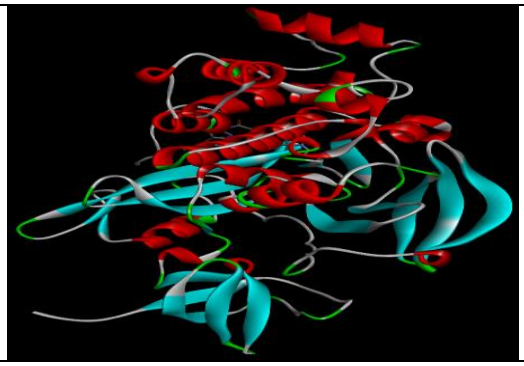
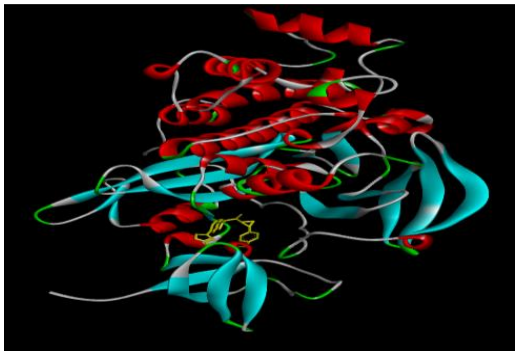
Table no 4: Anticancer Docking Score of Compounds with their image of docked complex.

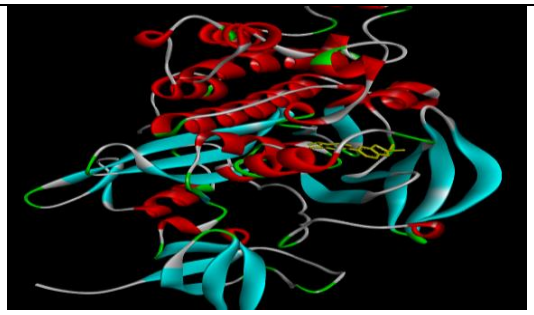
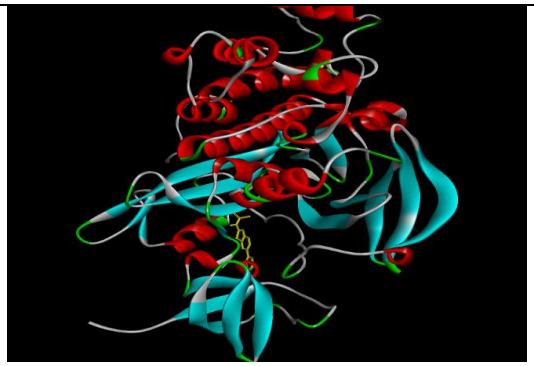
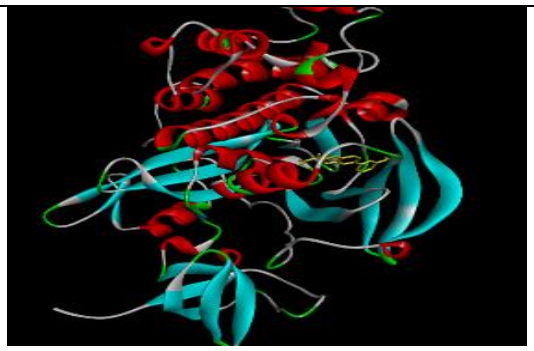
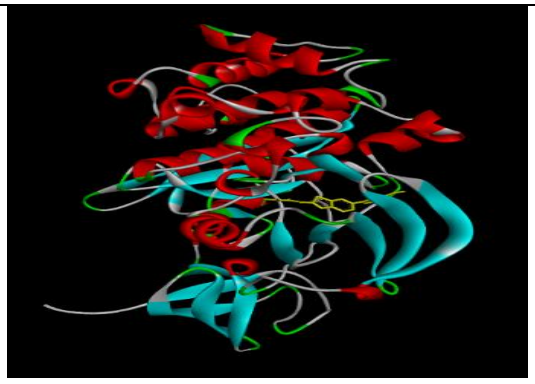
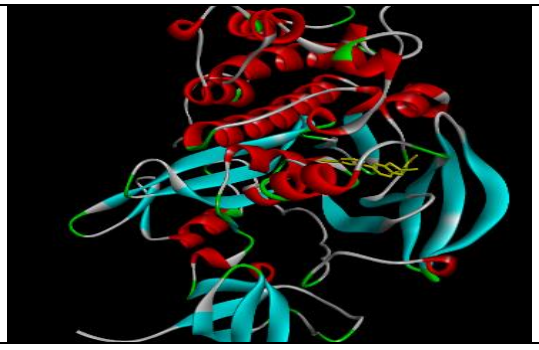
Compound code	Docking score	Docking image
1.	-6.37	
2.	-7.77	
3.	-8.34	

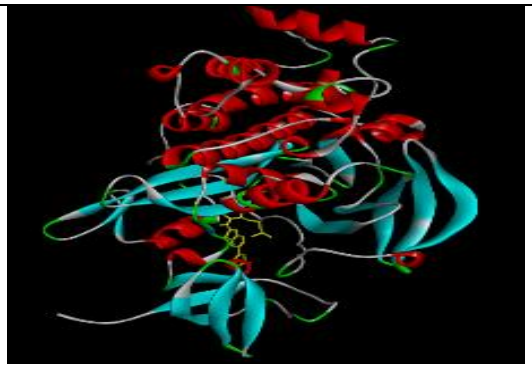
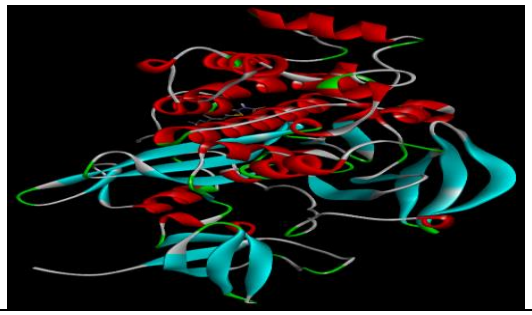
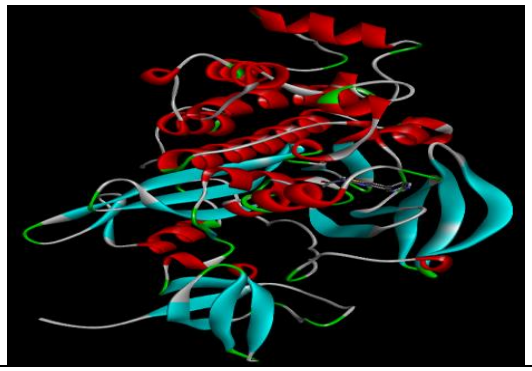
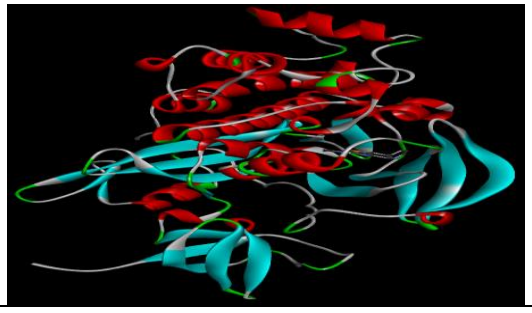
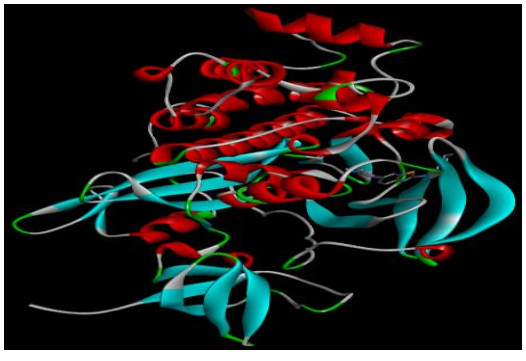
4.	-1.40	
5.	-8.10	
6.	-8.25	
7.	-0.79	
8.	-9.60	

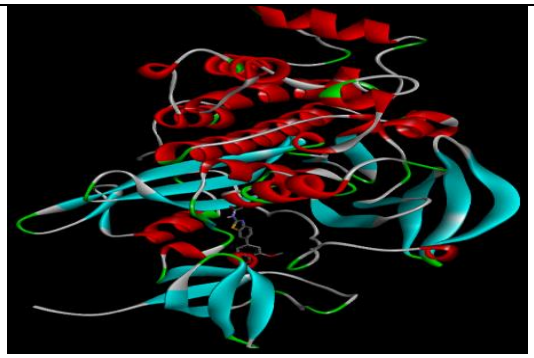
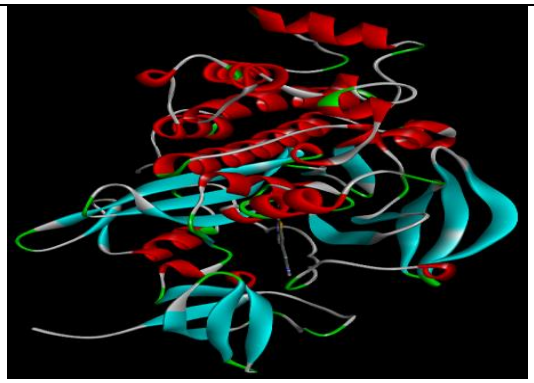
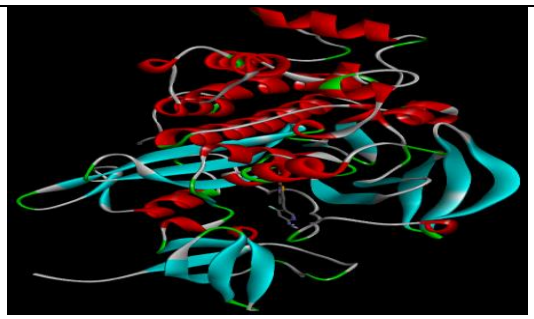
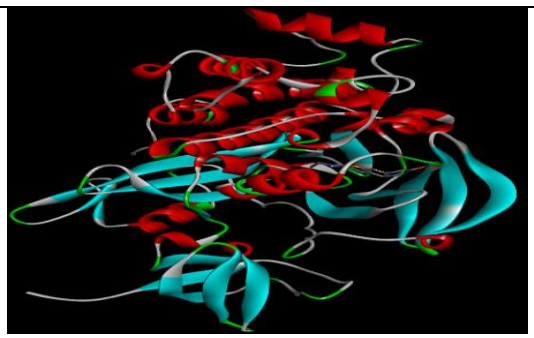
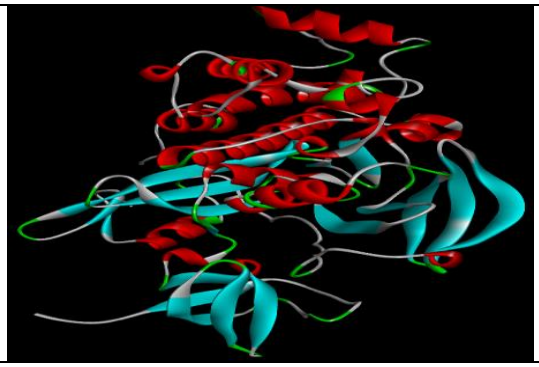
9.	-8.07	
10.	-9.70	
11.	-7.69	
12.	-9.06	
13.	-9.62	

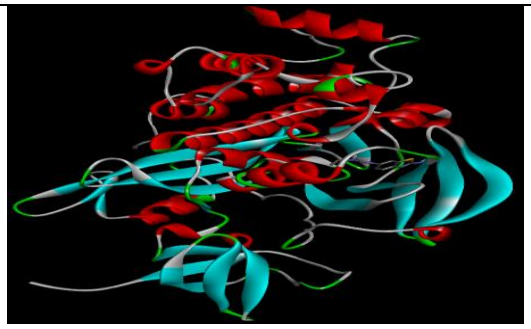
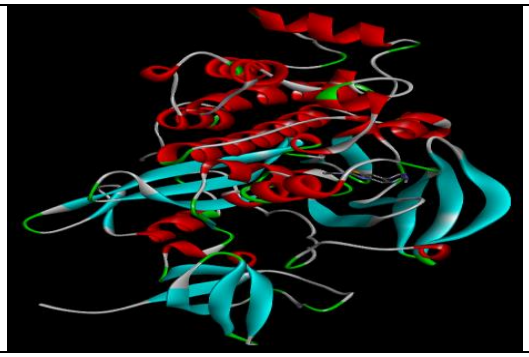
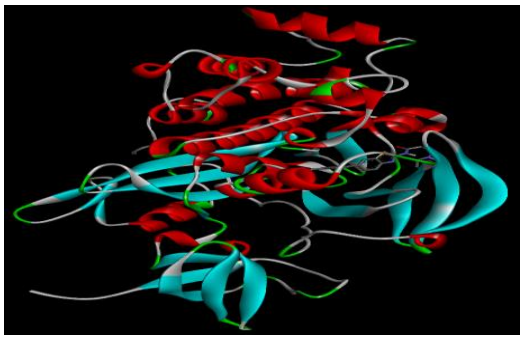
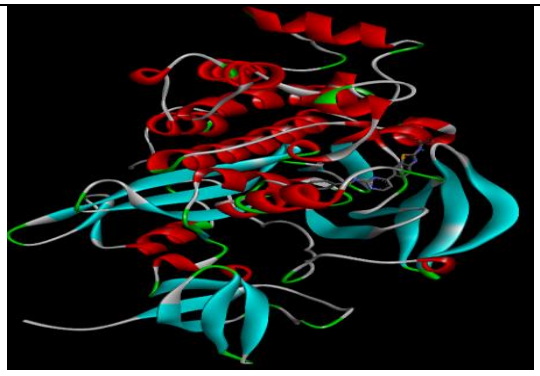
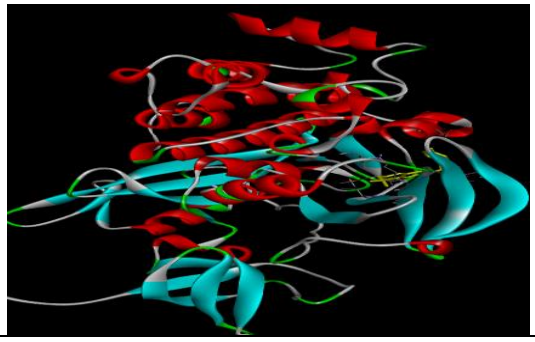
14.	-9.19	
15.	-10.24	
16.	-10.28	
17.	-8.95	
18.	-10.21	

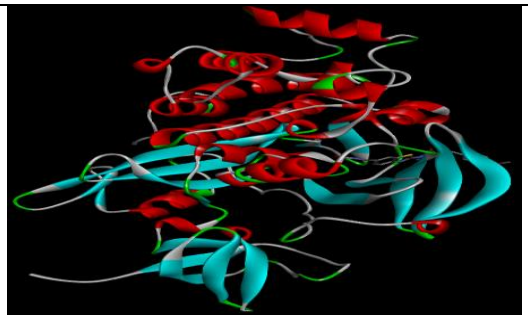
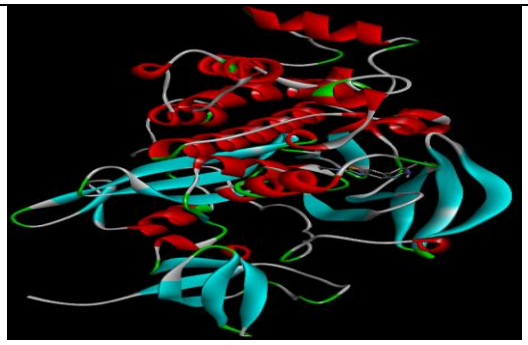
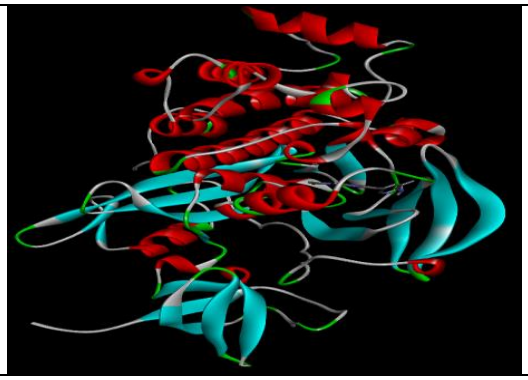
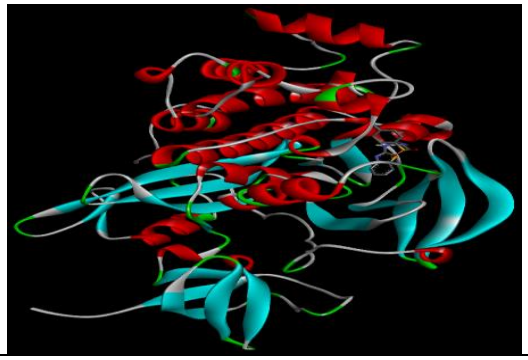
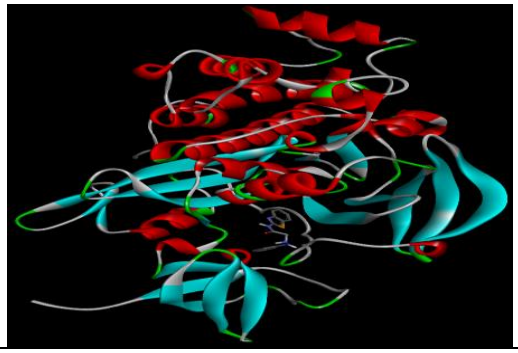
19.	-9.26	
20.	-10.05	
21.	-7.76	
22.	-9.24	
23.	-9.21	

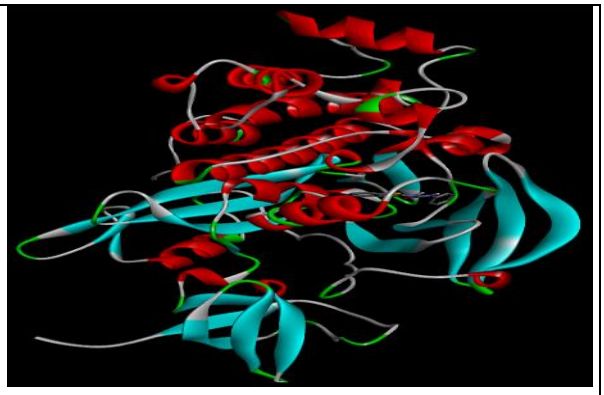
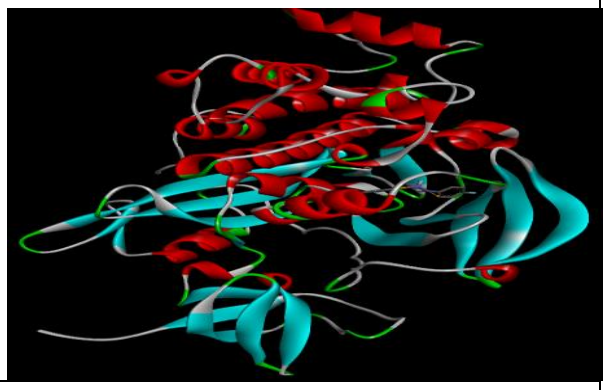
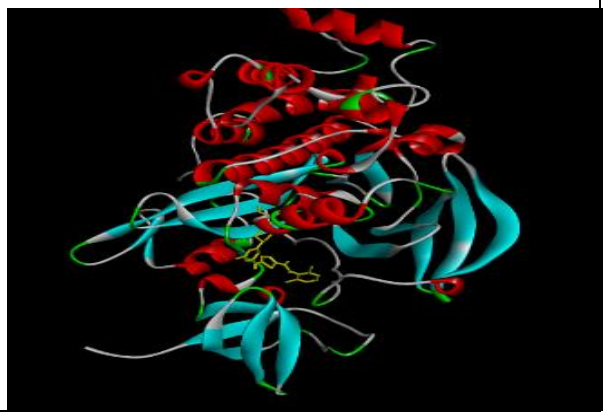
24.	-7.89	
25.	-7.9	
26.	-8.28	
27.	-9.26	
28.	-8.93	

29.	-8.1	
30.	-8.55	
31.	-9.19	
32.	-8.58	
33.	-9.05	

34.	-6.55	
35.	-7.26	
36.	-7.67	
37.	-8.83	
38.	-1.7	

39.	-7.94	
40.	-8.88	
41.	-8.55	
42.	-9.37	
43.	-6.94	

44.	-9.56	
45.	-9.74	
46.	-9.31	
47.	-7.87	
48.	-7.85	

49.	-8.49	
50.	-7.65	
51.	-8.00(STD)	

The AutoDock4 results revealed a broad distribution of binding energies among the screened compounds, ranging from −0.79 to −10.28 kcal/mol. A significant number of derivatives exhibited binding energies lower than the reference ligand (−8.00 kcal/mol), indicating stronger binding affinity toward the target protein. Several compounds demonstrated highly favorable interactions, with docking scores reaching up to −10.28 kcal/mol, indicating stable ligand–protein complexes.

The findings demonstrate that several designed analogues exhibit strong binding potential with effective interactions at the active site of the Tyrosine Kinase receptor.

5. ADMET EVALUATION

Pharmacokinetic evaluation of proposed ligands was done by the software ADMETlab3.0 for predicting the absorption, distribution, metabolism, excretion, and toxicity properties. The table showing ADMET profile of selected compound having the best docking score are given in table 7and 8.

Table 8: ADMET Profile of Selected Compounds.

Compound Code	Absorption (Caco-2 / PAMPA / HIA)	Distribution (BBB, PPB, VDss)	Metabolism (Transporter Inhibition)	Excretion (Cl)	Inhibitor	Substrate
B16	Caco-2 –4.63, PAMPA +, HIA +	BBB +, PPB 0.983, VDss 2.61	OATP1B1 +++, OATP1B3 +++, MRP1 +++	Moderate	Yes	No
B26	Caco-2 –4.92, PAMPA –, HIA –	BBB –, PPB 0.927, VDss 10.04	OATP1B1 ++, OATP1B3 +++, MRP1 +++	High	No	Yes
B36	Caco-2 –4.88, PAMPA –, HIA –	BBB –, PPB 0.963, VDss 1.90	OATP1B1 ++, OATP1B3 +++, MRP1 +++	Moderate	Yes	No
B18	Caco-2 –4.92, PAMPA –, HIA –	BBB –, PPB 0.985, VDss 2.36	OATP1B1 +++, OATP1B3 +++, MRP1 +++	Moderate	Yes	No
B31	Caco-2 –4.82, PAMPA –, HIA –	BBB –, PPB 0.963, VDss 1.50	OATP1B1 +++, OATP1B3 +++, MRP1 ++	High	Yes	No
B2	Caco-2 –5.53, PAMPA –, HIA –	BBB –, PPB 0.975, VDss 2.73	OATP1B1 ++, OATP1B3 +++, MRP1 ++	High	Yes	Yes
B46	Caco-2 –4.86, PAMPA –, HIA –	BBB –, PPB 0.954, VDss 2.67	OATP1B1 ++, OATP1B3 +++, MRP1 +++	High	Yes	Yes
B47	Caco-2 –4.63, PAMPA +, HIA +	BBB –, PPB 0.991, VDss 0.67	OATP1B1 +++, OATP1B3 +++, MRP1 ++	Moderate	Yes	No
B25	Caco-2 –4.36, PAMPA +, HIA +	BBB +, PPB 0.903, VDss 1.50	OATP1B1 +++, OATP1B3 +++, MRP1 ++	Moderate	Yes	Yes
B22	Caco-2 –4.87, PAMPA –, HIA –	BBB –, PPB 0.972, VDss 3.92	OATP1B1 ++, OATP1B3 +++, MRP1 +++	Moderate	Yes	Yes
B39	Caco-2 –4.64, PAMPA –, HIA –	BBB –, PPB 0.978, VDss 1.47	OATP1B1 ++, OATP1B3 +++, MRP1 ++	High	No	Yes
B30	Caco-2 –4.63, PAMPA +, HIA +	BBB –, PPB 0.986, VDss 0.98	OATP1B1 ++, OATP1B3 +++, MRP1 +++	High	No	Yes

Table 9: Safety & Toxicity Profile of Selected Compounds.

Compound Code	Toxicity	Cardiotoxicity	Hepatotoxicity	Carcinogenicity
B16	Low	No	Mild	No
B26	High	Yes	Severe	Yes
B36	Moderate	No	Mild	No
B18	High	Yes	Severe	Yes
B31	Moderate	Yes	Severe	Yes
B2	Moderate	Yes	Severe	Yes
B46	High	Yes	Severe	Yes
B47	Low	No	Mild	No
B25	Low	No	Mild	No
B22	Low	No	Mild	No
B39	Moderate	Yes	Severe	Yes
B30	Moderate	Yes	Severe	Yes

The ADMET evaluation of 2-aminobenzothiazole (2-ABT) derivatives in comparison with Dasatinib provides important insights into their pharmacokinetic behavior, safety profile, and overall drug-likeness. While Dasatinib is an effective tyrosine kinase inhibitor, its clinical utility is limited by pronounced toxicity, particularly cardiotoxicity (hERG inhibition), hepatotoxicity, and multi-organ adverse effects.

From a pharmacokinetic perspective, many derivatives maintain acceptable absorption and distribution characteristics, with predicted good intestinal permeability, suitable bioavailability, and balanced clearance profiles, indicating drug-like behavior comparable to the standard.

A major advantage of the analogues is the reduction in hERG inhibition, suggesting a comparatively lower risk of cardiotoxicity. Additionally, several compounds demonstrate reduced hematotoxicity and cytotoxicity, implying a safer therapeutic window with less bone marrow suppression. The lower promiscuity observed across most derivatives further indicates improved target specificity and reduced off-target interactions, which is critical for minimizing adverse effects.

Moreover, selected analogues exhibit reduced nephrotoxicity and neurotoxicity, supporting a comparatively improved multi-organ safety profile. Improvements in skin sensitization in certain compounds also suggest better tolerability.

Despite these advantages, limitations persist. Hepatotoxicity remains high and comparable to Dasatinib, representing a major class-wide concern. Similarly, genotoxicity is not significantly reduced, indicating potential long-term safety risks. In addition, the improvements are not consistent across all compounds, with some analogues still exhibiting elevated toxicity.

In summary, the 2-ABT derivatives offer clear advantages over Dasatinib in terms of cardiac safety, selectivity, and hematological profile, while maintaining acceptable pharmacokinetic properties. However, persistent hepatotoxicity and genotoxicity highlight the need for further structural optimization before clinical translation.

CONCLUSION

The present study demonstrates that 2-aminobenzothiazole (2-ABT) derivatives possess significant potential as novel anticancer agents, supported by an integrated in-silico evaluation combining molecular docking, ADMET profiling, and biological activity prediction. The docking analysis revealed that several analogues exhibit strong binding affinity toward the tyrosine kinase receptor, with binding energies surpassing that of the reference drug Dasatinib, indicating stable ligand–protein interactions and effective target engagement.

Pharmacokinetic assessment indicated that many derivatives possess favorable drug-like properties, including acceptable absorption, balanced distribution, and moderate clearance. Compliance with Lipinski’s rule of five further supports their suitability for oral bioavailability. Additionally, PASS predictions confirmed moderate to high probabilities of biological activity across the compound series, reinforcing their potential therapeutic relevance.

Importantly, the toxicity analysis highlights a key advantage of these analogues over Dasatinib. Several lead compounds demonstrated lower cardiotoxicity, reduced systemic toxicity, and absence of carcinogenicity, along with only mild hepatotoxicity, suggesting an improved safety profile and wider therapeutic window. Reduced promiscuity and manageable metabolic interactions further indicate better selectivity and lower risk of off-target effects.

Despite these promising findings, certain limitations persist, including variability in absorption, moderate protein binding, and residual hepatotoxicity in some compounds, indicating the need for further structural optimization. Moreover, the predictions remain computational and require experimental validation to confirm their pharmacological and toxicological behavior.

In conclusion, 2-aminobenzothiazole derivatives represent a promising scaffold for the development of next-generation tyrosine kinase inhibitors with improved safety and pharmacokinetic profiles. Their enhanced binding affinity, favorable ADMET characteristics, and reduced toxicity risks position them as strong candidates for further preclinical studies, structure–activity relationship optimization, and eventual therapeutic development in anticancer research.

ACKNOWLEDGEMENT

We wanted to offer this endeavour to GOD ALMIGHTY for all the blessings showered on us during the course of this research. I take the privilege to acknowledge all those who helped in the completion of the project. At first, we express a deep sense of gratitude and indebtedness to the Department of Pharmaceutical Chemistry of Mar Dioscorus College of Pharmacy for helping in the completion of our work. We are deeply obliged to Prof. Rachel Mathew, our guide as well as our mentor, for her guidance, immense knowledge, insightful comments, constant support, and encouragement, which helped us to complete the work within the time schedule. We express my sincere gratitude to Mrs. Vani V, Associate Professor and our co-guide for sharing her expertise by giving constructive comments and suggestions upon reviewing the study.

REFERENCES

1. Guang Huang, Tomasz Cierpicki, Jolanta Grembecka, 2-Aminobenzothiazoles in anticancer drug design and discovery, Bioorganic Chemistry, 2023; Volume 135, 106477. ISSN 0045-2068 https://doi.org/10.1016/j.bioorg.2023.106477.
2. Eshkil F, Eshghi H, Saljooghi AS, Bakavoli M, Rahimizadeh M.Benzothiazole thiourea derivatives as anticancer agents: design, synthesis, and biological screening. Russ J Bioorg Chem, 2017; 43(5): 576-582. doi: 10.1134/S106816201705006
3. Deore, AB, Dhumane JR, Wagh HV, Sonawane RB, The Stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development, 2019; 7(6): 62-67, DOI: http://dx.doi.org/10.22270/ajprd.v7i6.616
4. Sen DJJ, Chaudhary PK, Sharma UD, Oza MV, Raval DH, Chaudhary DP. “Molinspiration is inspiration to molecule by software in drug discovery.”
5. Ali Irfan, Fozia Batool, Syeda Andleeb Zahra Naqvi, Amjad Islam, Sameh M. Osman, Alessio Nocentini, Siham A. Alissa & Claudiu T. Supuran, Benzothiazole derivatives as anticancer agents, Journal of Enzyme Inhibition and Medicinal Chemistry, 2020; 35:1: 265-279, DOI: 10.1080/14756366.2019.1698036
6. Gao X, Liu J, Zuo X, Feng X, Gao Y. Recent advances in synthesis of benzothiazole compounds related to green chemistry. *Molecules,* 2020; 25(8): 1813. doi:10.3390/molecules25081813.
7. Ismail TI, El-Khazragy N, Azzam RA. In the pursuit of novel therapeutic agents: synthesis, anticancer evaluation, and physicochemical insights of novel pyrimidine-based 2-aminobenzothiazole derivatives. *RSC Adv,* 2024; 14(23): 16332–16348. doi:10.1039/D4RA01874E.

8. Yadav KP, Rahman MA, Nishad S, Maurya SK, Anas M, Mujahid M. Synthesis and biological activities of benzothiazole derivatives: A review. *Intelligent Pharmacy*, 2023; 1(3): 122–132. doi:10.1016/j.ipha.2023.06.001.
9. Javahershenas R, Han J, Kazemi M, Jervis PJ. Recent advances in the application of 2-aminobenzothiazole to the multicomponent synthesis of heterocycles. 2024; Published online 2024 Sep 9. doi:10.1002/open.202400185.
10. Huang G., Cierpicki T., Grembecka J. 2-Aminobenzothiazoles in anticancer drug design and discovery. Bioorganic Chemistry, 2023; 135: 106477. doi:10.1016/j.bioorg.2023.106477.
11. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2001;46(1–3):3–26
12. Lagunin AA, Stepanchikova AV, Filimonov DA, Poroikov VV. PASS: prediction of activity spectra for biologically active substances. *Bioinformatics*, 2000; 16(8): 747–748
13. Fu L, Shi S, Yi J, Wang N, He Y, Wu Z, et al. ADMETlab 3.0: an updated comprehensive online ADMET prediction platform enhanced with broader coverage, improved performance, API functionality and decision support. *Nucleic Acids Res*, 2024; 52(W1): W422–W431.
14. UCSF ChimeraX. Pettersen EF, Goddard TD, Huang CC, Meng EC, Couch GS, Croll TI, et al. UCSF ChimeraX: structure visualization for researchers, educators, and developers. *Protein Sci*, 2021; 30(1): 70–82.
15. PubChem. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Res*, 2021; 49(D1): D1388–D1395.
16. Avogadro. Hanwell MD, Curtis DE, Lonie DC, Vandermeersch T, Zurek E, Hutchison GR. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *J Cheminform*, 2012; 4: 17.
17. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem*, 2009; 30(16): 2785–2791.
18. Jejurikar BL, Rohane SH. Drug designing in Discovery Studio. Int J Sci Res Dev, 2021; 14(2): 135–138.
19. Rayan B, Rayan A. Avogadro Program for Chemistry Education: To What Extent Can Molecular Visualization and Three-Dimensional Simulations Enhance Meaningful Chemistry Learning? *World J Chem Educ*, 2017; 5(4): 136-141. doi:10.12691/wjce-5-4-4.
20. Sahu MK, Nayak AK, Hailemeskel B, Eyupoglu OE. Exploring recent updates on molecular docking: types, method, application, limitation and future prospects.