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Research Article

3D QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP DESIGNING AND MOLECULAR DOCKING STUDY OF NOVEL THIADIAZOLE DERIVATIVES AS A POTENTIAL ANTI-CANCER AGENT

INDHUMATHY P, GANDHIMATHI R*

Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India.
***Corresponding author: Gandhimathi R; Email: drgmathipharm2017@gmail.com**

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ABSTRACT

Objective: Melanoma, which arises from uncontrolled melanocyte growth, can be treated with surgery in the early stages but poses challenges in advanced cases. This study used 3D quantitative structure–activity relationship (3D QSAR) and docking methods to evaluate 51 molecules and to identify compounds with significant binding affinity to BRAF protein. The objective of this study is to design and evaluate novel thiadiazole derivatives as potential anti-cancer agents using a combination of 3D-QSAR modeling and molecular docking studies.

Methods: The study employs a 3D QSAR approach to analyze the inhibitory activity of 51 selected molecules against BRAF, a key target in cancer research. The methodology is structured as follows. A total of 51 molecules were retrieved from the literature based on their documented inhibitory activity against BRAF. These molecules were curated and preprocessed to ensure consistency and accuracy for further computational analysis. Molecular descriptors, which quantitatively represent molecular properties, were generated to facilitate the QSAR modeling process. These descriptors were essential for establishing a correlation between molecular features and biological activity. The Schrödinger software suite was employed to conduct the 3D QSAR analysis. The model was built using ligand-based and structure-based approaches, incorporating spatial and electronic properties to predict activity. To further validate the binding potential of these molecules, PyRx software was utilized for molecular docking studies. Docking simulations helped assess the binding interactions between the molecules and the BRAF protein, offering insights into potential drug-receptor affinity. This methodology allows for the identification of key structural features contributing to BRAF inhibition, providing a foundation for the design of more potent inhibitors in future research.

Results: The Gaussian-based QSAR was produced by correlating with the five fields of steric, electrostatic, hydrophobic, hydrogen bond donor (HBD), and hydrogen bond acceptor (HBA) with the aid of PLS with five variables. With a standard error estimate of 0.2 and an F ratio of 80.3, r^2cv values of 0.47 and r^2 0.93 were obtained. The steric, HBA, hydrophobic, HBD, electrostatic, and field contributions were, in order, 0.29, 0.08, 0.24, 0.18, and 0.188. Based on the structure of this best descriptor, novel 25 thiadiazole derivatives were designed. For these 25 novel molecules, a docking study was performed using PyRx software.

Conclusion: The results of this study indicate that the thiadiazole ring's (HBD) and (HBA) substituents are crucial to the drug's BRAF antagonistic action. Good r^2 = 0.93 was displayed by the Gaussian models that were developed based on the five field intensities. The docking studies revealed that the derivative IA25 (−9.7 k/cal) showed a similar binding affinity of standard molecule Dabrafenib toward the targeted protein and these molecules showed 2 conventional hydrogen bonds with Asn221 and Phe209 amino acid residues. The remaining compounds showed the docking score range from 8 k/cal to 9.6 k/cal. Based on the docking score 10 molecules are selected for further studies.

Keywords: Thiadiazole, BRAF enzyme, Quantitative structure–activity relationship, Docking studies.

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INTRODUCTION

Radiation, chemotherapy, surgery, and targeted medicines are among the treatments for cancer, which is one of the major causes of mortality globally [1]. Cancer treatment is still quite difficult, even with advances in medical technology. Globally, there were 9.6 million recorded fatalities and 18.1 million new cases in 2018 [2-4]. It is anticipated that the total number of new cancer cases would rise as the population ages and expands. With an expected 1.5 million new cases in 2020, skin malignancies are the most common type of cancer detected globally. Less frequently occurring than other forms of skin cancer, melanoma arises when melanocytes proliferate uncontrollably [5]. If not discovered and treated promptly, it has a higher chance of spreading to other areas of the body, making it more hazardous. In both normal and transformed cells, BRAF (Fig. 1), a serine/threonine protein kinase, is essential for the RAS-RAF-MEK-ERK mitogen-activated protein kinase cell signaling pathway, which transmits extracellular signals through the cell and alters gene expression, cell growth, survival, and differentiation [6-10].

Early-stage melanomas can be treated with surgery, but "advanced melanomas" are harder to treat [11,12]. "Newer immunotherapy and targeted therapy drugs, such as BRAF inhibitors," target cells with gene or protein changes in melanoma cells [13-17]. These drugs block the BRAF protein (Fig. 1), which is often mutated in melanoma cells, slowing or stopping cell growth [18]. Examples include dabrafenib (Fig. 2), sorafenib, and vemurafenib.

Thiadiazole, a five-member heterocyclic molecule with nitrogen and sulfur atoms, is found in four isoforms [19]. Its compounds have various pharmacological properties, including anti-viral, anti-fungal, anti-bacterial, anti-parasitic, anti-inflammatory, and anticancer activities. Thiadiazole (Fig. 3) is the bioisostere of pyrimidine and oxadiazole [20-22].

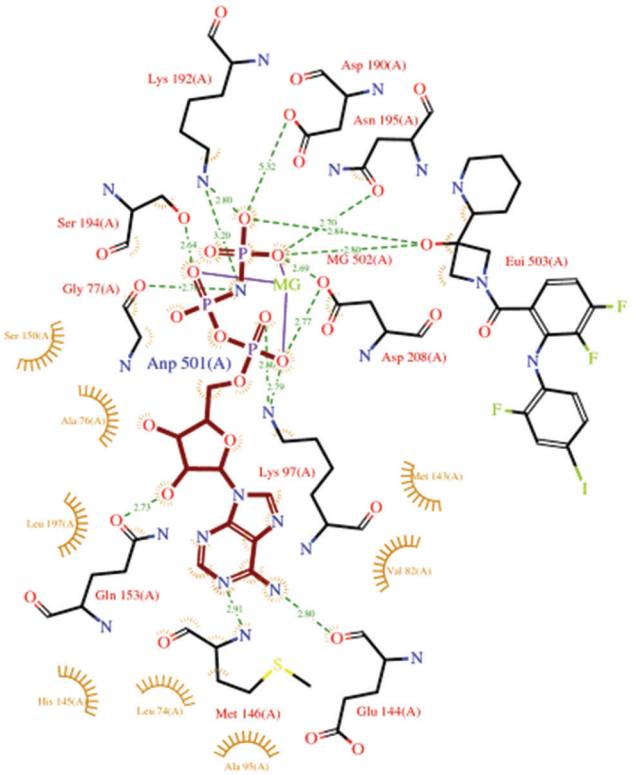

Fig. 1: BRAF Enzyme

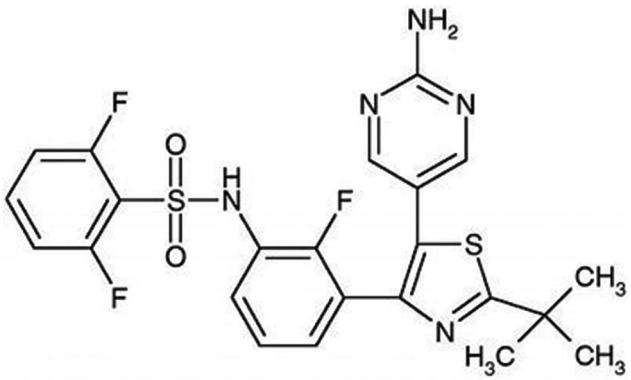

Fig. 2: Structure of Dabrafenib

Fig. 3: Structure of thiadiazole

Thiadiazole derivatives have shown promise as potential anti-cancer agents due to their structural similarity to pyrimidine and oxadiazole, as well as their broad-spectrum pharmacological activities. However, there is a lack of systematic research on their potential as BRAF inhibitors, particularly in the context of structure–activity relationship (SAR) studies and computational modeling.

Thus, the core research problem revolves around the design, computational modeling, and evaluation of novel thiadiazole-based inhibitors targeting BRAF using advanced 3D Quantitative SAR (3D QSAR) and molecular docking techniques. This study aims to bridge the gap by identifying new lead compounds with improved efficacy and selectivity against BRAF mutations in melanoma, ultimately contributing to the development of more effective targeted therapies.

METHODS

Dataset collection

The study's data collection involved obtaining 51 molecules with documented BRAF inhibitory activity from peer-reviewed literature, ensuring a diverse dataset for 3D QSAR modeling and molecular docking studies. Molecular descriptors, including hydrophobicity, electrostatic potential, and steric interactions, were generated using Schrödinger software to analyze the SAR. The dataset was divided into a training set (70%) for model development and a test set (30%) for validation, enhancing predictive accuracy. PyRx software was used for molecular docking, where each molecule's binding affinity and interactions with the BRAF active site were evaluated. The BRAF protein structure was sourced from the Protein Data Bank (PDB), whereas molecular data were retrieved from PubChem and literature reports. To ensure reproducibility, the study followed standardized computational protocols, cross-validation techniques, and publicly available datasets, allowing future researchers to verify and replicate the findings effectively.

QSAR studies

Dataset for analysis

51 compounds having BRAF inhibitory activity were included in the collection, and the literature was consulted for available half-maximum effective concentration (EC_{50}) data [23]. Biovia Drug Discovery Studio was used to sketch the compounds' structures. By taking a negative logarithm, the EC_{50} results from the cell-based assay were transformed into pEC_{50}. Based on a 4:1 ratio, the entire set of inhibitors was split into a test set (15 compounds) for validating the created model and a training set (36 compounds) for creating 3D-QSAR models. To obtain the optimal QSAR model, the dataset will be randomly divided over a number of cycles. "Then the best model will be selected, on the basis of partial least square (PLS) regression values" (R2, Q2, Pearson-R) [24]. The flow chart for the procedure is given below in the Fig. 4.

QSAR model generation

One of the prerequisites for generating a highly predictive 3D-QSAR model is the alignment of compounds that were used in the study. There are several alignment methods reported among them receptor-based alignment comparatively generates the best model. To determine the statistical association of activity versus chemical characteristics and to comprehend the biological significance of each fragment in the structure with the activity, we thought that receptor-based alignment was crucial in Gaussian QSAR models. The steric and electrostatic properties were used to create the field-based 3D-QSAR model. On the other hand, the characteristics of the Gaussian model comprised Gaussian hydrophobic, Gaussian steric, Gaussian electrostatic, and Hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) [25]. The entire set of inhibitors was divided into training and test sets for the purpose of creating and validating the models. The structural differences in the substitutions were automatically clustered to choose the optimal training set. These compounds were similarly distributed across the training and test sets, yielding appropriate Guassian-based 3D-QSAR models. Models with high r2 and q2 values were obtained using PLS analyses using all 51 chemicals for the Gaussian model in the training set with 5 PLS factors [26]. Table 1 lists the training and test compounds' experimental and anticipated half-maximal inhibitory concentration (IC_{50}) values for each model.

Gaussian-based 3D-QSAR model

3D-QSAR analysis was performed using the Schrodinger 9.2 version. By connecting with the established biological activities and 3D properties

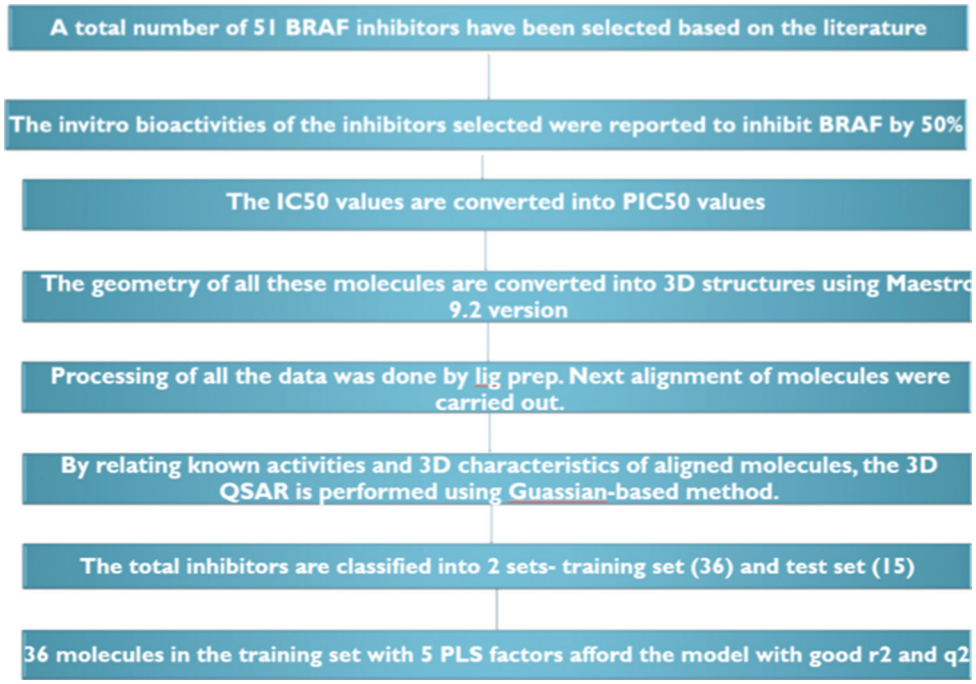

Fig. 4: Workflow for 3D quantitative structure–activity relationship model generation

Table 1: Experimental and predicted IC_{50} values for the set of 51 compounds

S. No	Experimental activity	Predicted activity	S. No	Experimental activity	Predicted activity
1	5.38	5.2	27	0.37	6.4
2	5.10	5.2	28	10	5
3	100	4	29	1.1	5.9
4	11.46	4.9	30	1.1	5.9
5	31	4.5	31	6.70	5.1
6	0.5	6.3	32	0.58	6.2
7	0.94	6.0	33	10	5
8	0.23	6.6	34	10	5
9	0.13	6.8	35	10	5
10	0.98	6	36	10	5
11	2.2	5.6	37	10	5
12	0.70	6.1	38	10	5
13	0.21	6.6	39	10	5
14	0.086	7	40	0.33	6.4
15	0.53	6.2	41	0.19	6.7
16	1.5	5.8	42	9.4	5.0
17	0.086	7	43	10	5
18	0.25	6.6	44	14	4.8
19	0.14	6.8	45	10	5
20	0.057	7.2	46	10	5
21	0.18	6.7	47	10	5
22	117	3.9	48	1.4	5.8
23	94	4.0	49	0.009	8.0
24	98	4.0	50	8.8	5.0
25	105	3.9	51	0.042	7.3
26	125	3.9			

IC_{50}: Half-maximal inhibitory concentration

of a collection of aligned molecules, the 3D-QSAR is utilized to build the model. Steric, electrostatic, hydrophobic, HBD, and HBA potential fields were used in the Gaussian 3D QSAR model interaction energy calculations. 3D-QSAR models were created using PLS regression analysis, where field and Gaussian intensities were utilized as descriptors and pIC_{50} values were employed as dependent variables. "Workflow for 3D-QSAR model generation 3D-QSAR model generation primary requirement is the alignment of all the molecules." Finally, the molecular descriptor with the best predicted IC_{50} value of the structure was observed (Fig. 5). Based on the structure [Fig. 7], novel compounds were designed. For those novel compounds molecular docking was performed.

Docking studies

Software used

In this research work, we used various bio-informatics tools to carry out for the work. In the current work we used following offline software's like Marvin sketch for sketching molecules, PyRx for performing the molecular docking studies, and some online software such as PDB, PubChem database, SPDBV, and Protein-ligand interaction profile (PLIP) [27].

Preparation of protein

We retrieved the targeted protein BRAF kinase (PDB ID: 4LMN) from the online program PDB website and the protein preparation was started from the removal of water molecules, and followed this we added the missing H-atoms, ionization and energy minimization of proteins. The energy minimization was done by applying force field through SPDBV software and it was validated by Ramachandran plot [28].

Identification of active sites

After the preparation of the protein, it was subjected to identify the active amino acid present in its structure by PLIP. Using PLIP we found the active amino acid residue present in the protein [29].

Preparation of ligands

The 3D and 2D structure of designed derivatives were sketched using Marvin sketch software. The sketched molecules are optimized and save as.pdb format for further processing.

Molecular docking

The PyRx software was used for the docking process. The docking process was performed using the molecular docking engine of PyRx using grid resolution. During the docking process, the default setting was used for the calculation [30,31].

RESULTS

Gaussian-based 3D-QSAR model

The five fields of "steric, electrostatic, hydrophobic, HBD, and HBA" were correlated using PLS with five variables to create the Gaussian-based QSAR. With a standard error estimate of 0.2 and an F ratio of 80.3, r^2cv values of 0.47 and r^2 0.93 were obtained, which is given in Table 2. The steric, HBA, hydrophobic, HBD, electrostatic, and field contributions were, in order, 0.29, 0.08, 0.24, 0.18, and 0.188 which is given in Table 3. In comparison to the "electrostatic, HBA, and HBD" field contributions, the "steric (0.29) and hydrophobic (0.24)" intensities showed larger field contributions, suggesting a greater steric and hydrophobic requirement for protein-ligand interactions. The graph was plotted with predicted IC_{50} values and experimental IC_{50} values are shown in Fig 6. or Gaussian-based 3D QSAR models, the expected correlation coefficients (r2) are 0.93, indicating that the Gaussian model prediction is accurate. .By comparison, of experimentally "observed and predicted IC_{50} values" of thiadiazole inhibitors, it can be seen that the "Gaussian model performed well in the prediction of activities for both training and test molecules." Eventually, using the anticipated IC_{50} value of compound 49 (Fig. 5) as a guide, 25 novel compounds as in Fig. 8 were created. It is evident from a comparison of the predicted and experimentally observed IC_{50} values that the Gaussian model did a good job of predicting the activities of both training and test molecules.

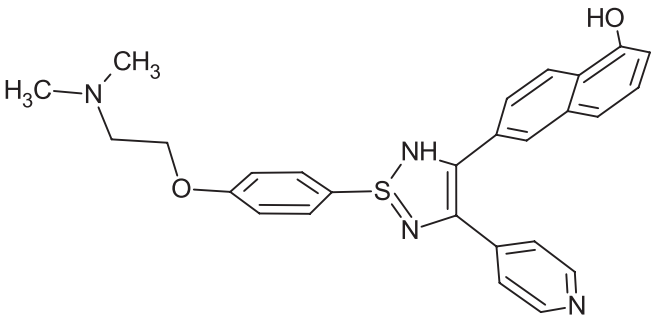

Fig. 5: Structure of compound 49

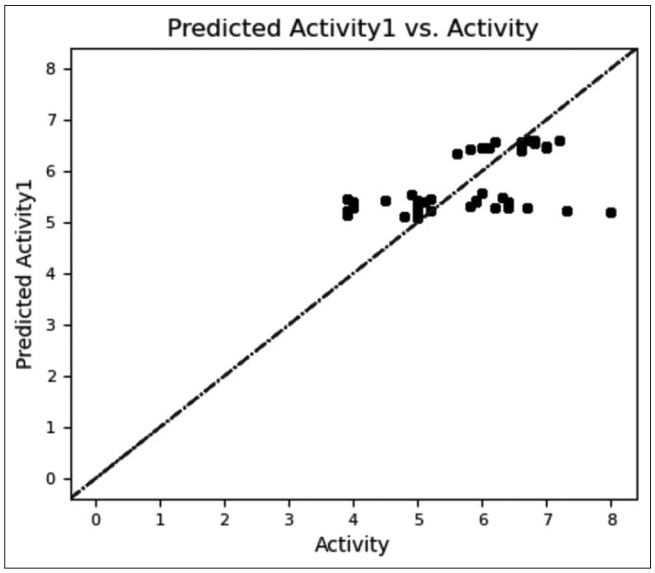

Fig. 6: Graph against Experimental activity versus predicted activity

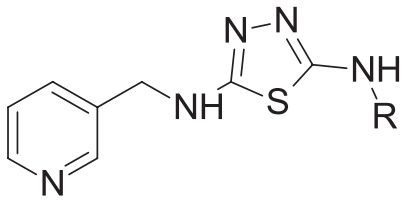

Fig. 7: Parent structure of dataset compounds

Molecular docking

We used the X-ray crystal structure of BRAF kinase (PDB ID: 4LMN) with high configuration was used for this current work. The selected enzyme is complex with GDC0973 (PDB ID: 4LMN) and the resolution is 2.80Å. The optimization and validation of the docking results were validated by the compared with the docking conformation of the parent inhibitor in the crystal structure. All the 25 designed molecules were docked against the active site of BRAF kinase enzyme and the free energy calculations are shown in Table 4 and the hydrogen bond and other interactions are shown in Figs. 9-11. The present study was compared with the previously reported anti-proliferative activity of the BRAF kinase inhibitor of dabrafenib. All the compounds show the common van der Waals bond with following amino acids such as Lys97, Ile99, Gly128, Phe129, Ile141, His188, Arg189, Val211, Leu215, and Gly210. Among the 20 studied compounds, the derivative IA25 (−9.7 k/cal) showing a similar binding affinity of standard molecule Dabrafenib towards the targeted protein and these molecules show 2 conventional hydrogen bonds with Asn221 and Phe209 amino acid residues. Remaining all the compound showed the docking score range from 8 k/cal to 9.6 k/cal. Based on the docking score 10 molecules are selected for the further studies.

DISCUSSION

The results of this study demonstrate that thiadiazole derivatives have promise as BRAF inhibitors for the treatment of melanoma [32]. The 3D

Table 2: Statistical parameters

S. No	PLS Statistics	Values
1.	SD	0.2630
2.	R2	0.9305
3.	R2CV	0.4777
4.	R2CV SCRAMBLE	0.6791
5.	STABILITY	0.6522
6.	F	80.3
7.	P	1.895e-16

Table 3: Statistical parameters of field contributions

S. No	Field contributions (%)	Values
1	Steric	0.2952
2	Electrostatic	0.0873
3	Hydrophobic	0.2492
4	HBA	0.1802
5	HBD	0.1881

HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor

Table 4: Docking score

Compound code	Free binding energy	Compound code	Free binding energy
IA1	−9.2	IA14	−9.3
IA2	−9	IA15	−8.5
IA3	−8	IA16	−8.6
IA4	−9.1	IA17	−8.7
IA5	−8.6	IA18	−8.7
IA6	−8.9	IA19	−8.9
IA7	−8.7	IA20	−9.2
IA8	−9.1	IA21	−8.9
IA9	−9.3	IA22	−9.1
IA10	−9.5	IA23	−8.5
IA11	−9.5	IA24	−9.6
IA12	−9.3	IA25	−9.7
IA13	−9	Dabrafenib	−10.4

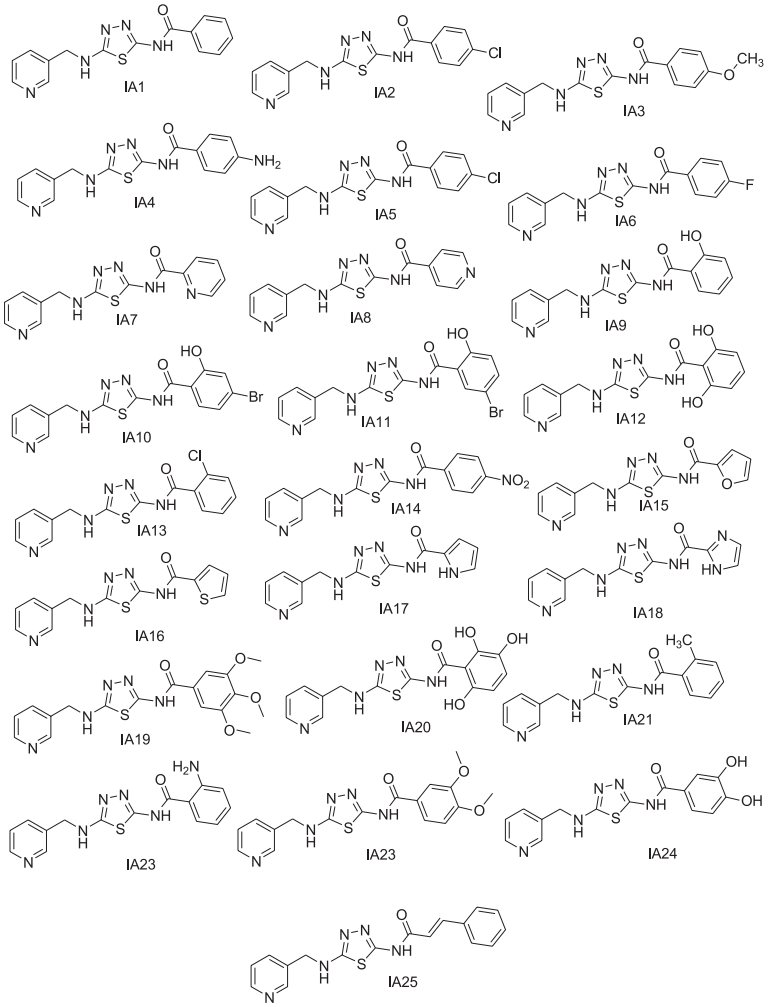

Fig. 8: Newly designed thiadiazole derivatives

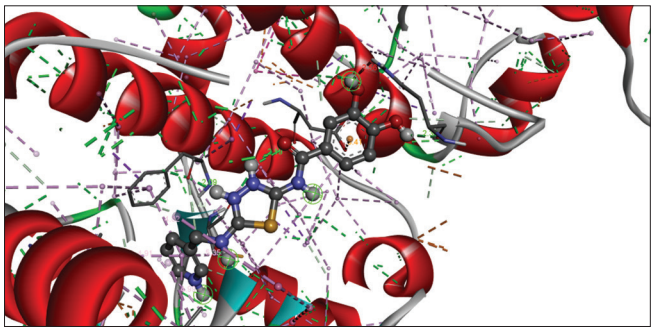

Fig. 9: 3D interaction of compound IA24 against BRAF kinase

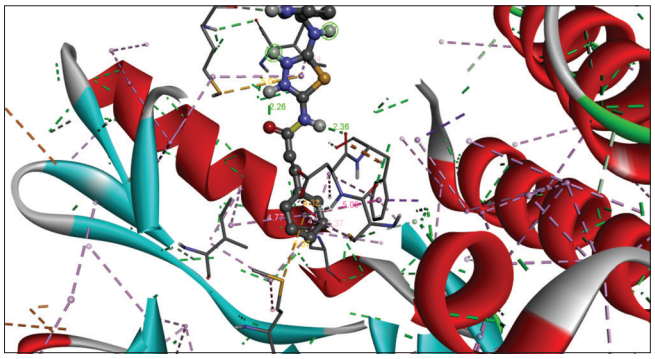

Fig. 10: 3D interaction of compound IA25 against BRAF kinase

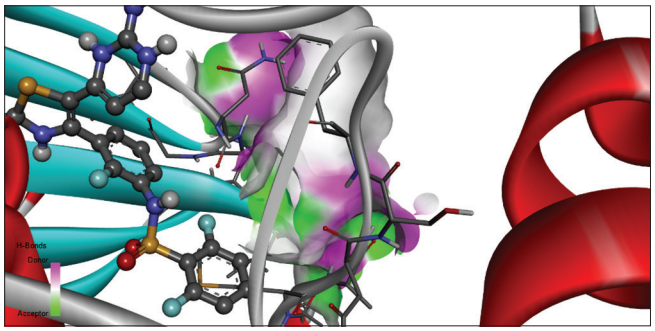

Fig. 11: 3D interaction of Dabrafenib against BRAF kinase

QSAR analysis revealed important chemical descriptors that contribute to potency and offered insightful information on the structural and electronic characteristics required for increased inhibitory efficacy [33]. These results were further supported by molecular docking experiments employing PyRx, which showed that certain drugs had substantial binding affinities with the BRAF kinase active site [34]. A significant potential for therapeutic use is suggested by the interactions that have been identified between thiadiazole derivatives and important amino acid residues within the binding pocket.

FUTURE SCOPE

To evaluate the effectiveness, toxicity, and pharmacokinetics of identified BRAF inhibitors, future research will concentrate on experimental validation through and experiments. By taking protein

flexibility into account, molecular dynamics simulations can increase docking accuracy. Predictive accuracy can be improved by using machine learning models and adding more BRAF inhibitors to the dataset. More effective treatments can be developed by looking into the mechanisms underlying drug resistance and investigating multi-target therapy. Furthermore, clinical partnerships and AI-driven drug development can hasten the translation of computational results into practical medicinal uses.

CONCLUSION

In summary and conclusion, this study indicates that the thiadiazole ring's (HBD) and (HBA) substituents are crucial to the drug's BRAF antagonistic action. This information aids in recommending substituents that will increase the drug's biological activity and selectivity against BRAF. Good r^2 = 0.93 was displayed by the Gaussian models that were developed based on the five field intensities. Furthermore, 25 novel compounds with strong anticancer properties can be designed using the models created here. For those novel compounds molecular docking was performed. The docking result revealed that all the compounds easily interact with the active amino acid residue of the studied BRAF protein. The docking studies revealed that the studied compounds, the derivative IA25 (−9.7 k/cal) showing similar binding affinity of standard molecule dabrafenib toward the targeted protein and these molecules show 2 conventional hydrogen bonds with Asn221 and Phe209 amino acid residues. Remaining all the compound showed the docking score range from 8 k/cal to 9.6 k/cal. Based on the docking score 10 molecules are selected for the further studies.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study. All authors have read and accepted the published version of the manuscript**.**

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The authors declare that they have no funding support for the study.

DATA AVAILABILITY

All relevant data are within the paper.

ETHICAL APPROVAL

No ethical approval was required for this study. Informed Consent This study did not involve the participation of human subjects, so no ethical approval or informed consent was required.

RESEARCH INVOLVING HUMAN AND ANIMAL RIGHTS

The corresponding author affirms, on behalf of all authors, that human and animal rights were upheld in the study. Moreover, this study did not involve human or animal participation.

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