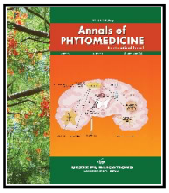
Annals of Phytomedicine 12(1): 318-324, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.1.37

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Molecular docking, ADME analysis, and pharmacophore modelling of benzoxazole fused azetidinone derivatives as antibreast cancer agents

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Article Info

Article history

Received 15 February 2023

Revised 6 April 2023

Accepted 7 April 2023

Published Online 30 June-2023

Keywords

Benzoxazole

Breast cancer

Molecular docking

Pharmacophore

Abstract

Breast cancer is the most common cancer among women worldwide. In this study, different derivatives of benzoxazole-coupled azetidinone (DJ1-DJ20) were designed and investigated for antibreast cancer activity targeting a newly recognized receptor, PPARG (PDB:1FM9). These derivatives were designed with varying properties of substituent, such as hydrogen bonding ability, hydrophilicity, hydrophobicity, steric, and electronic effects. Firstly, designed compounds (DJ1-DJ20) were docked with receptor PPARG (PDB:1FM9), and the docking score was in the range of -5.180 to -8.485 kcal/mol. For further analysis, compounds having maximum interaction with receptors were selected based on the docking score greater than 7.5 kcal/mol. The selected compounds MM/GBSA, ADMET properties, pharmacophore modelling, and antibreast cancer properties were evaluated using computational tools, respectively. Among all the compounds, DJ10 showed the best interaction with receptors with the highest dock score of -8.485 kcal/mol and molecular mechanics with a generalized born and surface area solvation (MM/GBSA) score of -72.09 kcal/mol. Apart from these, all-selected compounds' physiochemical and druggable properties were within prescribed limits and adhered to Lipinski's rule of five and rule of three. Pharmacophore modelling showed the presence of steric and electronic features in the ligands to have supramolecular interaction with the PPARG receptor to produce a biological response. Finally, the selected compound's antibreast cancer properties were evaluated using PASS online tool to be antibreast cancer molecules with the highest possibility for compound DJ10 with a pharmacological active value of 0.293.

1. Introduction

Breast cancer is the most common and highest death-causing cancer among women globally (Tan *et al*., 2012; Dwivedi *et al.*, 2021). In 2020, 2.3 million new cases (11.7%) were reported for breast cancer among females. Global Cancer Statistics Society stated that breast cancer had surpassed lung cancer as the most common cancer (Bashar and Begam, 2022; Thuan Loi *et al.*, 2022). There are different methods for screening breast cancer, such as mammography and magnetic resonance imaging (MRI). However, women having breast cancer are presently treated with radiation or chemotherapy. During treatment, a small population of breast cancer cells fail the treatment and have self-renewal and stem-cell differentiation properties, which cause tumour recurrence and metastasis (Lukong, 2017). There are several risk factors associated with breast cancer, such as sex, age, estrogen, family history, gene mutations, and an unhealthy lifestyle (Yasheshwar *et al.*, 2022; Akram *et al.*, 2017; Naeem *et al.*, 2019).

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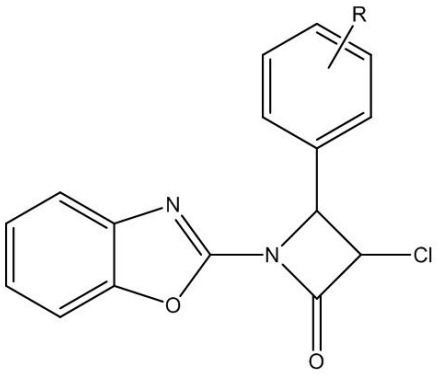
Epidemiological research also states that impaired glucose tolerance and type 2 diabetes have increased the risk of cancer (Dwivedi *et al.*, 2021). Therefore, it is essential to regulate lipid and glucose homeostasis, adipocyte differentiation, and intracellular insulin-signalling activities is the nuclear hormone receptor known as peroxisome proliferator-activated receptor gamma (PPARG) (Ferre, 2004; Szychowski *et al.*, 2017). Any mutation in PPARG affects the onset and cause of cancer and has been the subject of several studies. Keeping this in view, PPARG (PDB:1FM9) was selected as the target receptor for this study (Fu *et al.*, 2020; Tang *et al.*, 2015). Presently, we do not have a molecule to target this receptor and evaluate its effect.

As one of the most significant classes of heterocyclic compounds, benzoxazoles exhibit a wide range of biologically active properties, such as antimicrobial (Kaplancikli *et al.*, 2004; Saundane *et al.*, 2012), anticancer (Farag *et al.*, 2022; Khajondetchairit *et al.*, 2017), anti-inflammatory, antihistamine (Gurav *et al.*, 2022; Aggarwal *et al.*, 2017), and anti-Parkinson's (Anas *et al.*, 2022; Mohammadpoor-Baltork and Abdollahi-Alibeik, 2003). These heterocyclic molecules have properties to interact with receptors efficiently by forming different bonds. Apart from these, azetidinone, a four-membered heterocyclic ring, has also proven powerful pharmacological effects as an anticancer agent. For this reason, recent research has focused

more on the compound azetidinone and evaluates its anticancerous properties. Based on the afore mentioned information, the current study was created with the intention of designing different substitutes for a novel series of 2-amino benzoxazole combined with azetidinones and evaluating its binding properties to the PPARG receptor against breast cancer.

2. Materials and Methods



R = H, 4-iso CH_3, 4-Br, 4-C1, 2,5-OCH_3, 2-OH, 3-$N0_2$, 2-OCH_3, 4-(Dimethylamino), 3,5-Cl, 2-OH-5 OCH_3, 3-CHO, 3-OCH_3, 3,4,5-OCH_3, 3-C1, 4-OH, 4-$N0_2$, 4-F, 4-(benzyloxy), 4-OH-3-OCH_3

Figure 1: Designed compounds with their substituents.

2.1 Design of ligands and selection of receptor

In this study, different substituted amino benzoxazole combined azetidinones (DJ1-DJ20) ligands were designed with varying properties of the substituents, as shown in Figure 1. Further, this compound's-molecular docking, ADME analysis, and pharmacophore modelling, and structure-activity prediction were performed and evaluated for breast cancer properties. In the course of the study, we selected the disease target using the DisGeNET.org website and predicted particular ligands target using (swiss target prediction). The most common gene targets were obtained using the venny 2.0 tool, and it concluded that the PPARG receptor (PDB ID:1FM9) is most appropriate, and further, it was downloaded from the rcsb.org portal.

2.2 Molecular docking

All the design 2D ligands were designed using ChemDraw 20.0 tool, and their canonical smiles were generated and docked against the PPARG receptor (PDB ID: 1FM9). The receptor1FM9 had 2.1 Å resolution.Single chain A, sequence length is 238 amino acid residues and no mutation.It is pre-complex with 9-cis retinoic acid and GI262570 and co-activator peptides. The docking was performed using the maestro tool on the Schrödinger platform. In the process of docking, the first lig prep file was prepared, and then the preparation of protein was performed using protein preparation. During protein preparation, missing side chains and missing loops using prime were added, and it was optimized. Lastly, the receptor grid was generated and docked in the grid to obtain docking scores of the designed compounds DJ1-DJ20. Further, based on the highest docking score of compounds will be selected, and their other features will be calculated (Dwivedi *et al.*, 2021).

2.3 Prime MMGBSA

Prime MMGBSA reports many different energy properties of ligand, receptor, and receptor-ligand-complex concerning binding and strain within them. It estimates the free energy available to each other. It was performed using Schrödinger 2020-4 Prime module; it computed the total free energy in Bind (kcal/mol), compromise of molecular mechanics energies, and solvation of polar and nonpolar residue.

2.4 ADME properties and pharmacophore modelling

Determination of the ADME properties of molecules gives initial information on the druggable nature of molecules. It predicts the physicochemical properties of the compounds and features of Lipinski's rule of five, such as hydrogen bond donors and acceptors and log P value which are essential parameters for a molecule to be biologically active. In this study, the QikProp module of the Schrödinger suite 2022-4, was used to determine ADME properties of the selected compounds docked designed ligands (Rajagopal *et al*., 2020). Further, the top docked designed molecules pharmacophore modelling was performed using e-pharmacophore generation to understand the minimum feature of this ligand to have supra interaction with the receptor. This was performed using phase pharmacophore models (Schrodinger 2020-4: Phase) and showed the feature of ligand possesses for functional interaction with the receptor.

2.5 Prediction of biological activity using PASS online

The selected compounds were evaluated for antibreast cancer activity using the online tool prediction of activity spectra for substances (PASS). The PASS provides Pa (pharmacologically active) and Pi (pharmacologically inactive) values by uploading the canonical smiles of compounds. Pa (pharmacologically active) value is the possibility of compounds belonging to a particular class of compounds. The greater the Pa value higher the chance to belong to that class of compound (Verma *et al.*, 2019).

3. Results

3.1 Molecular docking

The ligands benzoxazole fused azetidinone derivatives (DJ1-DJ20) were designed with varying substitutions to have a different binding pattern to receptor PPARG. The receptor PPARG (PDB:1FM9) was predicted using venny 2.0 tool based on the data from the Swiss target prediction and disease target. Designed molecules were docked with receptor PPARG and showed docking scores in the range of -5.180 to -8.485 kcal/mol, as shown in Table 1.

Apart from these lists and amino acid and different bonds of interaction is mentioned in Table 2. The 2D and 3D interaction pattern of the top three docked compounds DJ10,D15, DJ1 is shown in Figures 2, 3, 4, respectively.

3.2 Prime MMGBSA

In a similar manner, free binding energy for selected molecules with target receptor 1FM9 was calculated using a prime MM-GBSA simulation run. The binding energy for selected compounds was in the range of -58.71 to -80.34 kcal/mol. Among all these compounds. All the parameters of MM/GBSA findings of selected compounds are reported in Table 3.

Table 1: Molecular docking scores of designed compounds (DJ1-DJ20)with PPARG receptor

Compounds	R-group	Docking score	Compounds	R- group	Docking score
DJ1	H	-8.20	DJ11	2-OH-5-OCH_3	-7.71
DJ2	4- CH_3	-6.42	DJ12	3-CHO	-5.18
DJ3	4-Br	-5.57	DJ13	3-OCH_3	-7.12
DJ4	4-Cl	-7.79	DJ14	3,4,5-OCH_3	-5.68
DJ5	2,5-OCH_3	-6.97	DJ15	3-Cl	-8.28
DJ6	2-OH	-6.42	DJ16	4-OH	-6.54
DJ7	3-NO_2	-6.10	DJ17	4-NO_2	-6.22
DJ8	2-OCH_3	-7.50	DJ18	4-F	-6.92
DJ9	4-$N(CH_3)_2$	-5.93	DJ19	4-(OC_6H_5)	-6.70
DJ10	3,5-Cl	-8.48	DJ20	4-OH-3-OCH_3	-7.00

Table 2: List of amino acids and interacting bonds of selected compounds with PPARG receptor

Compounds	Hydrophobic interaction	Polar interactions	Hydrogen interaction residue	Positive charged interactions	Negative charged interactions
DJ1	Ile249, Ile262, Leu255, Met348, Met364, Leu353, Met334, Ile281, Cys285, Phe287, Leu330, Val339, Ile341	Ser342	Ser342	Arg288	Glu359
DJ4	Ile281, Phe282, Cys285, Leu465, Tyr473, Leu469, Tyr327, Ile326, Met364, Phe363, Phe360, Leu356, Leu353, Leu453, Ile456	Gln286, Ser289, Hie323, Hie449	-	Lys367	-
DJ8	Ile281, Cys285, Ile326, Tyr327, Leu330, Leu333, Val339, Leu340, Ile341, Met348, Leu353, Met364	Ser289, Hie323, Ser342, Hie449	-	Lys367	-
DJ10	Ile281, Phe282, Cys285, Ile326, Tyr327, Leu330, Leu353, Leu356, Met364, Phe363, Phe360, Ile456, Leu453, Leu465, Leu469, Tyr473	Hie323, Ser289, Hie449, Gln286	-	Lys367	-
DJ11	Ile249, Leu255, Ile262, Ile281, Cys285, Phe287, Ile341, Val339, Leu330, Met334, Met364, Leu353, Met348	Ser342	Ser342	Arg280, Arg288	Glu259
DJ15	Ile249, Ile281, Cys285, Phe287, Leu255, Ile262, Met348, Leu353, Met364, Met334, Leu330, Val339, Ile341	Ser342	Ser342	Arg280, Arg288	Glu259

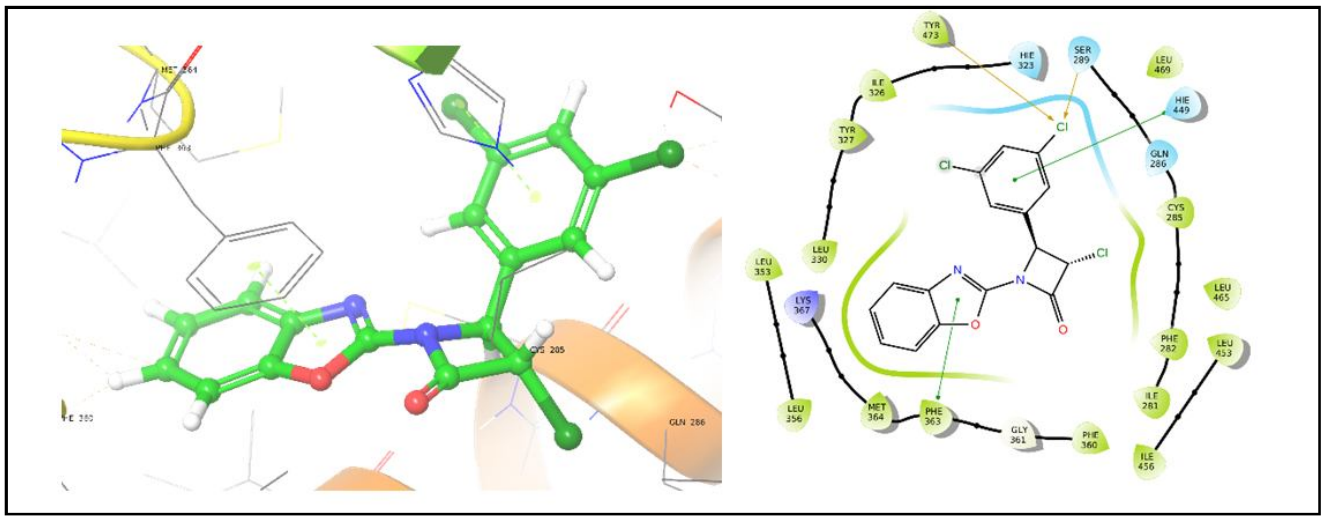


Figure 2: 3D and 2D interaction of compound DJ10 with 1FM9.

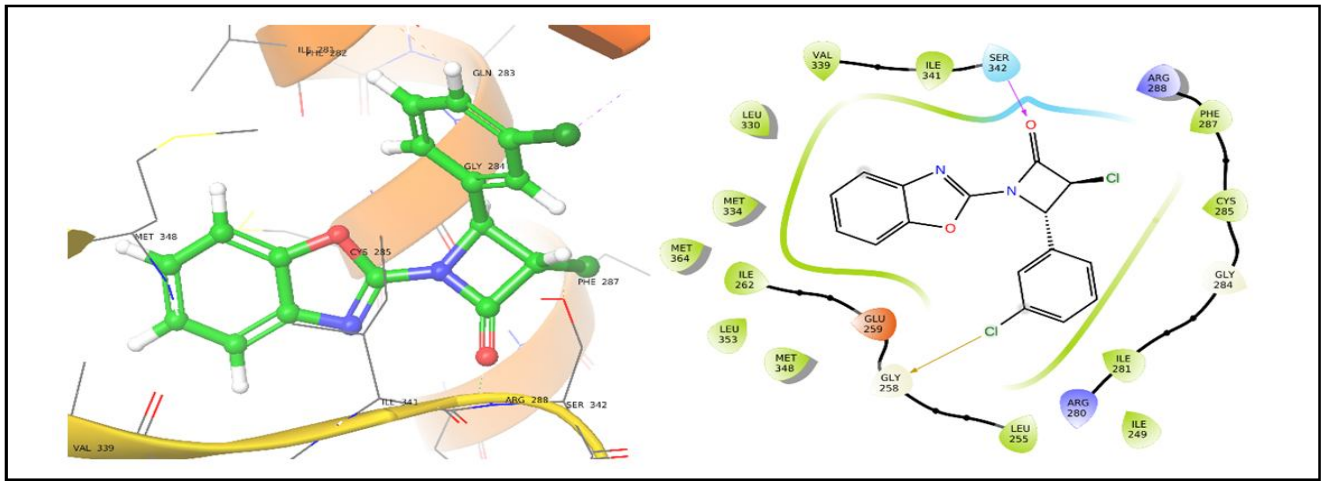


Figure 3: 3D and 2D interaction of compound DJ15 with 1MF9.

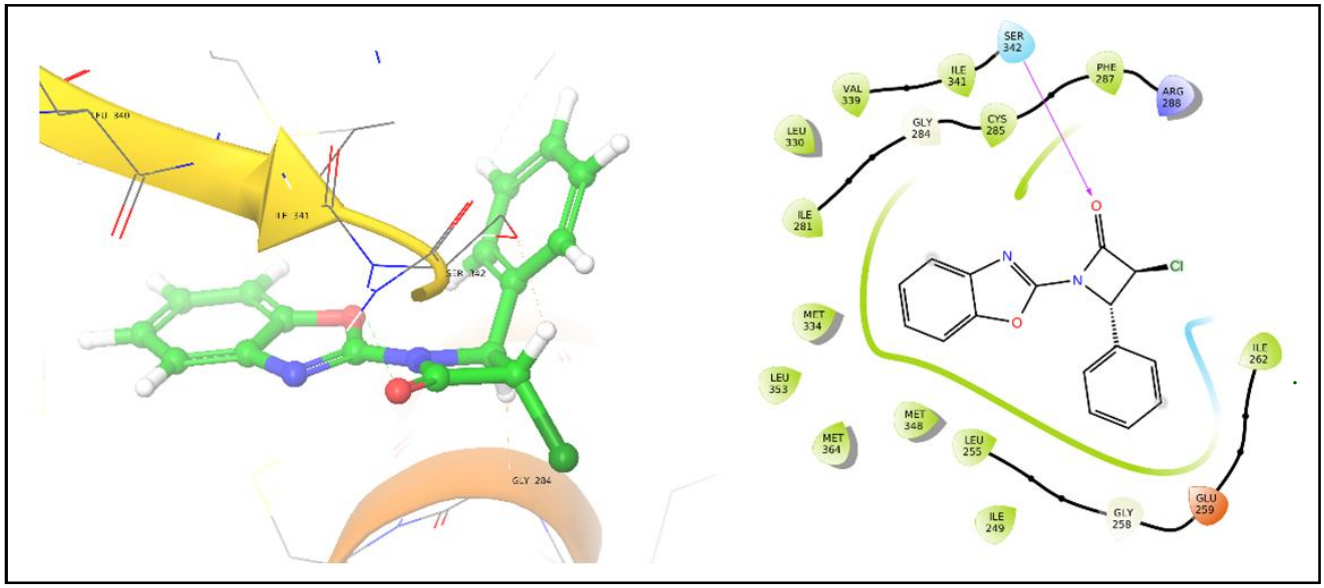


Figure 4: 3D and 2D interaction of compound DJ1 with 1FM9.

Table 3: Binding free energy calculation of selected compounds with PPARG receptor

Compounds	MMGBSA ΔG bind	MMGBSA ΔG bind coulomb	MMGBSA ΔG bind lipo	MMGBSA ΔG bind covalent	MMGBSA ΔG bind solv GB	MMGBSA ΔG bind vdW
DJ1	-68.22	-12.42	-34.16	2.45	13.84	-37.67
DJ4	-58.71	4.25	-51.25	7.89	13.59	-27.52
DJ8	-80.34	-8.25	-45.20	2.72	14.22	-43.10
DJ10	-72.09	-1.38	-56.69	9.95	10.43	-28.64
DJ11	-68.09	-10.32	-37.56	6.98	15.13	-42.05
DJ15	-76.57	-11.70	-40.88	2.74	13.11	-39.57

*Above parameters are in kcal/mol; ΔG bind: free energy of binding; ΔG bind lipo: Hydrophobic energy; ΔG bind coulomb: Coulomb energy; ΔG bind covalent: Covalent energy; ΔG bind solv GB: Generalized Born

3.3 ADME properties and pharmacophore modelling

The selected compound's physiochemical properties and druggable features were calculated using the QikProp module of the Schrödinger suite 2020-4. For selected compounds, molecular weight ranged from 298.72 to 344.75, the number of donors of hydrogen bonds ranged from 0 to 1, the number of acceptors of hydrogen bonds ranged from 4 to 5, partition coefficient ranged from 3.18 to 4.55. Based on the predicted results, it was observed that these compounds effectively satisfied all the parameters to be a druggable molecule and also obeyed Lipinski's rule of five and rule of three perfectly. The physicochemical properties of the selected compounds are reported in Table 4. Further, structural and chemical features of the molecules responsible for supra-interaction with receptors to produce biological responses were studied, generating pharmacophore modelling using e-pharmacophore generation from the phase module. The generated pharmacophore modelling, as shown in Figure 5.

Table 4: Predicted ADME profile of selected compounds

Compounds	MW	DH	AH	QPlogP (o/w)	Rule of five
DJ1	298.72	0.000	4.00	3.54	0
DJ4	333.17	0.000	4.00	4.05	0
DJ8	328.75	0.000	4.75	3.68	0
DJ10	367.61	0.000	4.00	4.55	0
DJ11	344.75	1.000	5.50	3.18	0
DJ15	333.17	0.000	4.00	4.06	0

MW: Molecular weight of the molecule (Recommended range: 130-500); DH: Predicted no. of hydrogen bonds that the solute in an aqueous solution would provide to water molecules (Recommended range: 0-6); AH: Predicted Number of hydrogen bonds that the solute in an aqueous solution would receive from the water molecules (Recommended range: 2-20);QPlogP (o/w): Calculated octanol/water partition coefficient (Recommended range: -2.0-6.5);Rule of five:Number of times Lipinski rule of five has been disobeyed. The rules are MW < 500, DH<5, AH<10, QPlogP (o/w) <5. Compounds that satisfy these rules are considered drug-like (Recommended range: maximum 4 violations).

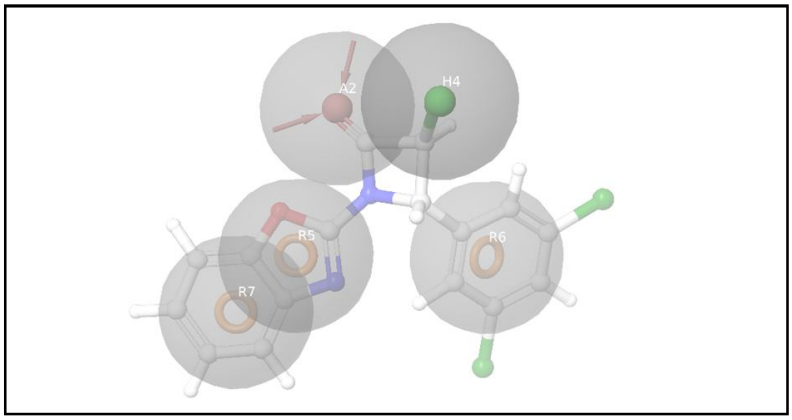


Figure 5: Predicted pharmacophore with their electronic and steric features.

3.4 Prediction of biological activity using PASS online

Finally, the selected molecules were subjected to biological activity using PASS online tool. The compounds Pa (pharmacologically active) was in the range of 0.259 to 0.293. Pa values for selected were compared and shown in Figure 6.

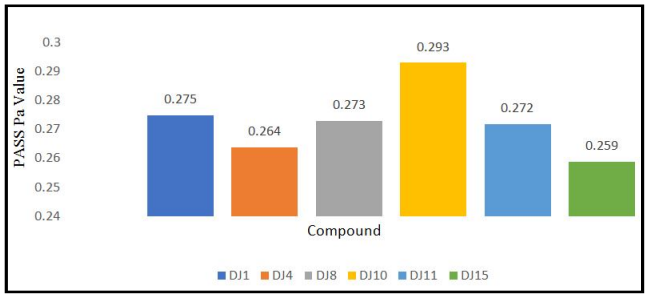


Figure 6: Predicted antibreast cancer property of selected molecules using thePASS online tool.

4. Discussion

Compound DJ10 (1-(benzo[d]oxazol-2-yl)-3-chloro-4-(3,5-dichlorophenyl) azetidine-2-one) showed the highest docking score of -8.485 kcal/mol. It interacted with various amino acids of the receptor by forming different bonds such as Pi-Pi stacking with Hie449, Phe363 and two halogen bonds with Ser289, Tyr473 hydrophobic interactions with Ile281, Phe282, Cys285, Ile326, Tyr327, Leu330, Leu353, Leu356, Met364, Phe363, Phe360, Ile456, Leu453, Leu465, Leu469, Tyr473 and polar interactions with Hie323, Ser289, Hie449, Gln286. As per MMGBSA run, DJ8 has the highest binding energy of 80.34 kcal/mol, whereas the top-docked compound DJ10 has a binding energy of -72.09 kcal/mol. And ADME parameter of DJ10 is under the range and it obeys the Lipinski rule of five further its pharmacophore were generated and it reveals that aromatic rings R5, R6, and R7, hydrogen bond acceptor A2, and hydrophobic H4 of the compound have excellent interaction with the receptor. The PASS online also showed the highest PA value for compound DJ10.

5. Conclusion

In this study, twenty different substituted benzo oxazolyl coupled azetidinone moieties (DJ1-DJ20) were designed based on enumeration with the varying steric and electronic features of the substituent and planned to screen for antibreast cancer targeting PPARG receptor (PDB:1FM9). The proposed receptor was selected using venny 2.0 tool based on the data obtained from the disease DisGeNET.org website and Swiss target prediction.The designed compounds (DJ1-DJ20) were docked with selected receptors, and the docking score was in the range of -5.180 to -8.485 kcal/mol. For the further computational exploration of antibreast cancer, properties of the compound having dock score greater than 7.5 kcal/mol were selected, and their interaction pattern to the PPARG receptor, ADME properties, prime MMGBSA, pharmacophore modelling, and PASS online studies were performed. The selected compounds were DJ1, DJ4, DJ8, DJ10, DJ11, and DJ15; among these compounds, DJ10 showed the highest dock score of -8.485 kcal/mol. The study showed a great interaction pattern, with good binding energy and glide score. The selected compounds' ADME and other druggable qualities fell well within the prescribed limit and obeyed Lipinski's rule and rule of three. Further, pharmacophore models showed that these designed compounds have the steric and electronic features to have supra-interaction with PPARG receptors to produce antibreast cancer properties. Finally, selected compound antibreast cancer properties were evaluated using PASS online tool. The Pa value from PASS online predicted that these designed compounds have a greater chance to belong to the antibreast cancer class of drugs with the highest of best-docked compounds DJ10. Thus, this study showed that benzo-oxazolyl coupled azetidinone moieties are a potential candidate for antibreast cancer. Further, to validate their predicted antibreast cancer capabilities, these designed ligands have to be synthesized and tested against the cell line to become promising leads for the treatment of antibreast cancer targeting PPARG receptors.

Acknowledgments

The authors are thankful to NGSM Institute of Pharmacy and Nitte (Deemed to be University) for providing the necessary facilities to carry out this research.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Gupta Dheeraj, Pankaj Kumar, Kavita Apte, Harsha Ashtekar, Seshagiri R Dixit (2023). Molecular docking, ADME analysis, and pharmacophore modelling of benzoxazole fused azetidinone derivatives as antibreast cancer agents. Ann. Phytomed., 12(1):318-324. http://dx.doi.org/10.54085/ap.2023.12.1.37.**