Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 9s, https://carcinogenesis.com/

Multicomponent Synthesis Of Triazole Derivatives Act As Potent Anti-Breast Cancer

Mr. Omkar U. Wagh[1], Miss. Priyanka A. Shelke[2], Mr. Dhanraj P. Saware[3], Ms.Vaishnavi V. Ingale[4], Ms. Dhanashri J. Desai[5], Dr. Prashant S. Misal[6], Dr Bhalchandra A. Kadam[7]

[1,2,5,] Assistant Professor, ASPM's K. T. Patil College of Pharmacy, Dharashiv.

[3]Assistant Professor, SCSSSAS Vasant Pharmacy College, Kaij.

[4]Assistant Professor, TPCT College of Engineering, Dept. of Pharmacy, Dharashiv.

[6]Associate Professor, Shri Ganpati Institutes of Pharmaceutical Sciences and Research, Tembhurni.

[7]Associate Professor, ASPM's K. T. Patil College of Pharmacy, Dharashiv.

ABSTRACT

Breast cancer continues to be a major global health challenge, driving the need for the discovery of novel and more effective therapeutic agents. Heterocyclic compounds, particularly 1,2,3-triazoles, have emerged as privileged scaffolds in medicinal chemistry due to their broad pharmacological profile, stability, and favorable drug-like properties. In this study, a series of novel triazole derivatives were synthesized through a multicomponent reaction (MCR) strategy, providing an efficient, atom-economical, and environmentally friendly approach for the rapid construction of structurally diverse molecules.

The synthesized compounds were characterized using standard spectroscopic techniques (FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry). The triazole derivatives were then evaluated for their anticancer potential against breast cancer cell lines (e.g., MCF-7, MDA-MB-231) using MTT assay and other relevant biological evaluations. Several derivatives demonstrated significant cytotoxic activity, with selectivity towards cancerous cells compared to normal cells. Structure–activity relationship (SAR) analysis indicated that electron-donating and heteroaryl substitutions on the triazole ring enhanced anticancer potency.

Overall, this study highlights the potential of multicomponent-synthesized triazole derivatives as promising anti-breast cancer agents, providing valuable insights for future drug discovery and development.

KEYWORDS: *Multicomponent reaction, 1,2,3-Triazole derivatives, Breast cancer, Anticancer activity, Heterocyclic compounds.*

How to Cite: Omkar U. Wagh, Priyanka A. Shelke, Dhanraj P. Saware,Vaishnavi V. Ingale, Dhanashri J. Desai, Prashant S. Misal, Bhalchandra A. Kadam., (2025) Multicomponent Synthesis Of Triazole Derivatives Act As Potent Anti-Breast Cancer, *Journal of Carcinogenesis*, *Vol.24, No.9s*, 202-212.

1. INTRODUCTION

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among women worldwide. Despite significant advancements in early detection and therapeutic strategies, the development of resistance, limited efficacy, and undesirable side effects of conventional therapies necessitate the search for novel, more effective, and safer anticancer agents. In this context, heterocyclic compounds have gained immense attention due to their structural diversity and broad spectrum of biological activities.

Among heterocycles, 1,2,3-triazoles represent an important pharmacophore in medicinal chemistry, owing to their stability, hydrogen bonding ability, and versatile biological activities including anticancer, antimicrobial, antiviral, and anti-inflammatory properties. The triazole ring can serve as a bioisostere of amide or ester linkages, enhancing pharmacokinetic properties and improving receptor binding interactions. Moreover, several triazole-based drugs are already in clinical use, highlighting their therapeutic relevance.

The multicomponent synthesis (MCRs) approach offers a powerful, time- and cost-efficient method for the construction of complex heterocyclic scaffolds in a single step, with high atom economy and structural diversity. The use of MCRs for designing triazole derivatives provides access to novel molecular architectures with improved drug-like properties. These methods are environmentally friendly and allow rapid generation of compound libraries for biological screening.

In the present study, we report the design and multicomponent synthesis of novel triazole derivatives and evaluate their potential as anti-breast cancer agents. The synthesized compounds were subjected to preliminary biological screening against breast cancer cell lines to explore their efficacy. This investigation aims to identify promising triazole-based leads that may contribute to the development of new therapeutic options for breast cancer management.

2. METHOD

Chemistry

The synthetic route to the desired 4-(((6-(4,5-diphenyl-1H-imidazol-2-yl) benzo[d][1,3] dioxol-4- yl) oxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives is summarized in Scheme 1. The deprotection 7-methoxybenzo[d][1,3] dioxole-5-carbaldehyde (1) which on treated with cold HI to give the compound of 7-hydroxybenzo[d][1,3] dioxole-5-carbaldehyde (2). Propargylation of compound (2)using propargyl bromide (3) dry DMF and dry K2CO3 room temperature for 3hrs to afford 7-(prop-2-yn-1-yloxy)benzo[d][1,3]dioxole-5-carbaldehyde (4) of reacted with various aryl azides(5a-j) at rt 4hrs the terminal alkyne position to obtain 7-((1-phenyl-1H-1,2,3-triazol- 4-yl)methoxy)benzo[d][1,3]dioxole-5-carbaldehyde(6a-j). One pot three component reaction of compounds (6a-j), benzil (7) and ammonium acetate in the presence of catalytic amount of acetic acid in methanol under reflux 69°C for 4hrs yields 4-(((6-(4,5-diphenyl-1H-imidazol-2- yl)benzo[d][1,3]dioxol-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazole (8a-j). The final compound obtained from compounds (8a-j) reacted with methyl iodide in presence of NaH in DMF at 00C 4 hrs to obtain our desired compounds (9a-j). The products were obtained in good yields (70- 80%).

Scheme:

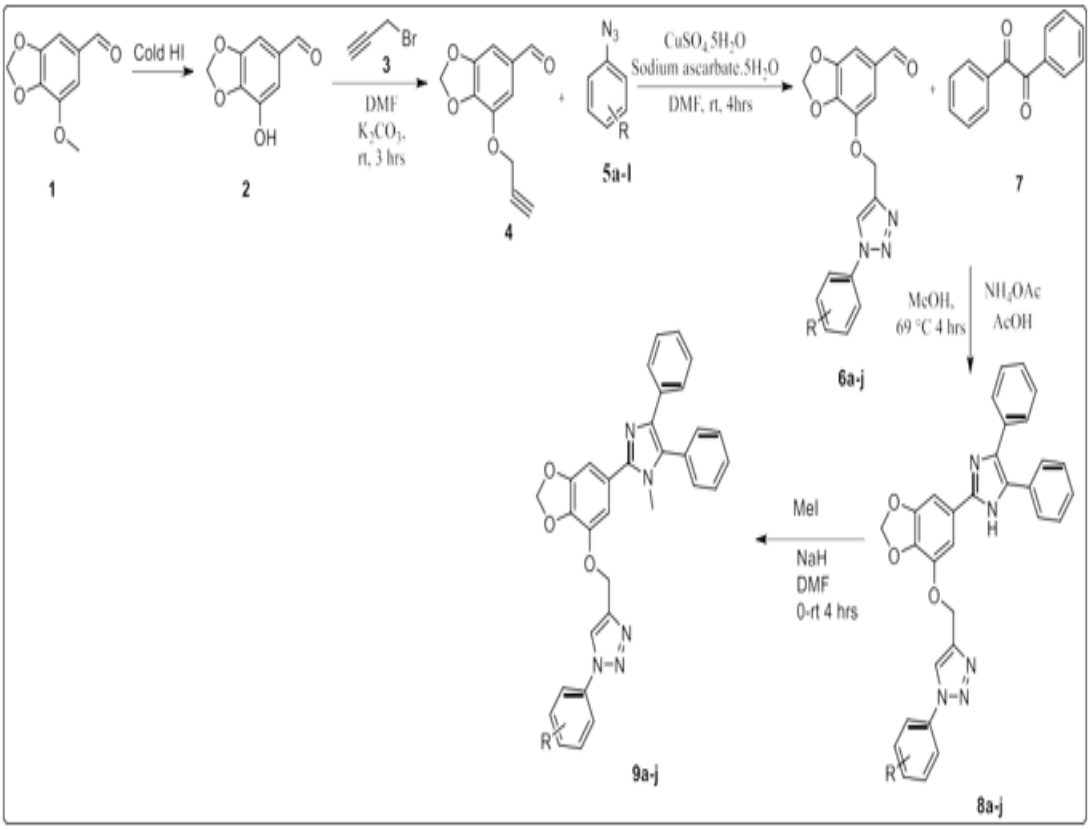
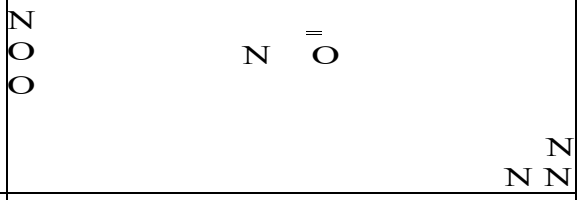
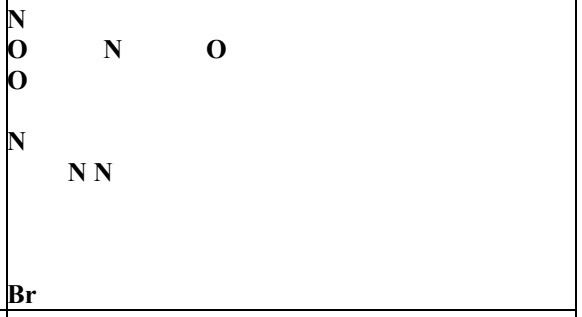
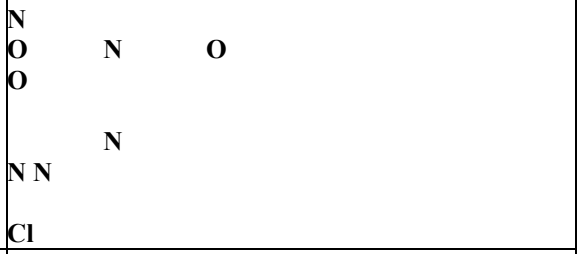
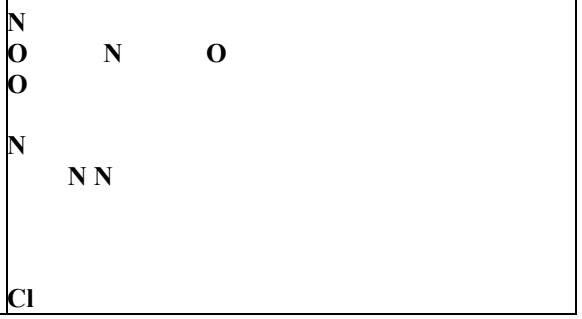
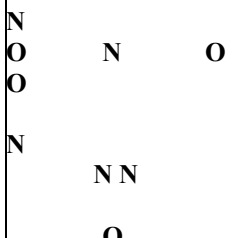
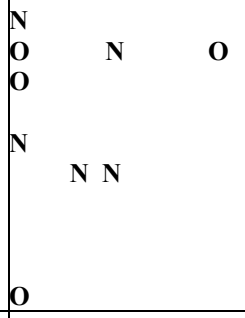
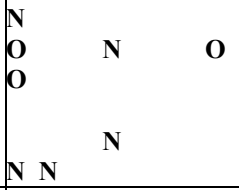
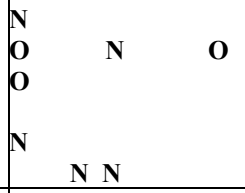
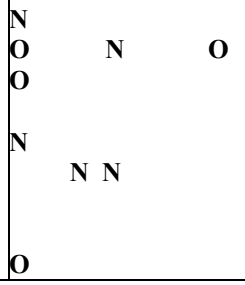


Table: Data of synthesized compounds (8a-j)

Sr. No.	LigandName	% Yield	Mol Formula	Structure
1	8a	70	C32H25N5O3	
2	8b	78	C32H24BrN5O3	
3	8c	71	C32H24ClN5O3	
4	8d	80	C32H24ClN5O3	

5.	**8e**	**81**	**C33H27N5O4**	
6.	**8f**	**76**	**C33H27N5O4**	
7	**8g**	**72**	**C33H27N5O3**	
8	**8h**	**85**	**C33H27N5O3**	
9	**8i**	**78**	**C34H27N5O4**	

10	**8j**	**73**	**C32H24N6O5**	**N O N O O N N N O2N**

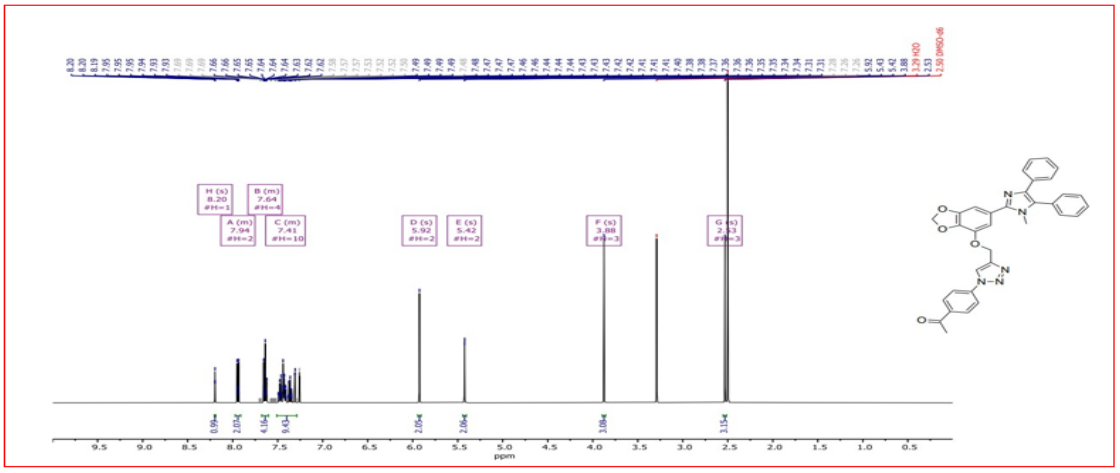


Fig: ^{1}H NMR 1-(4-(4-(((6-(1-methyl-4,5-diphenyl-1H-imidazol-2 yl)benzo[d][1,3]dioxol-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one(9i)

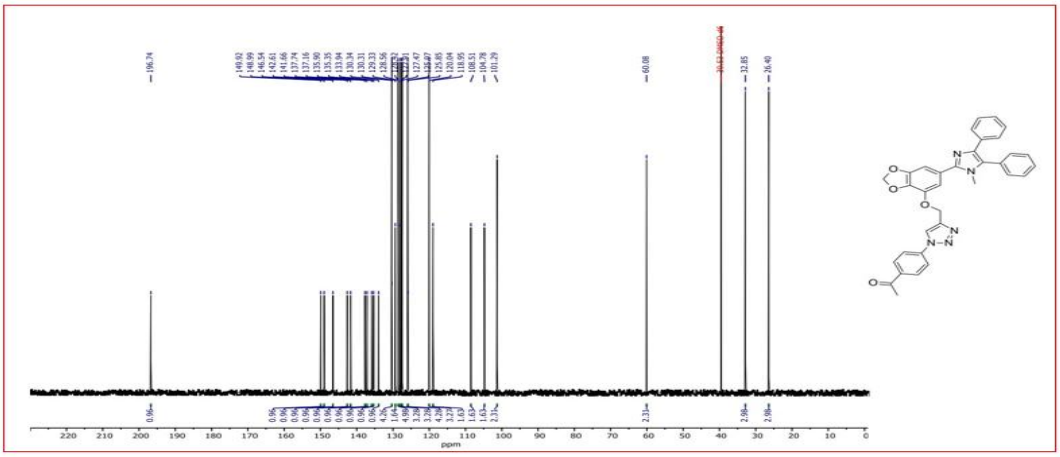
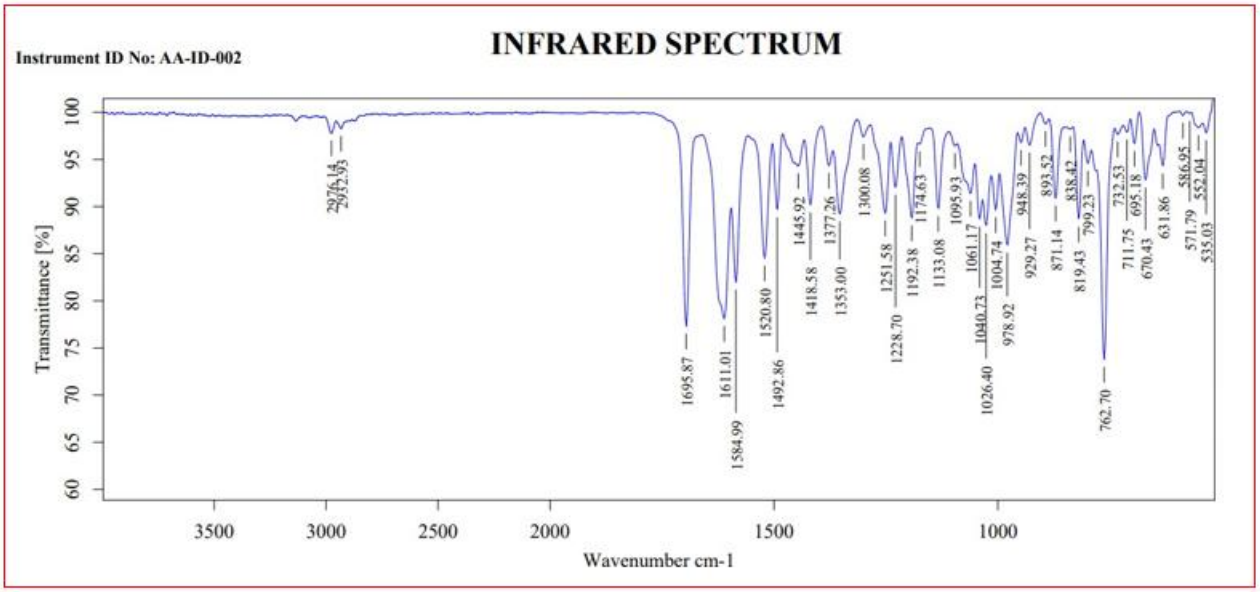


Fig: ^{13}CNMR 1-(4-(4-(((6-(1-methyl-4,5-diphenyl-1H-imidazol-2-yl)benzo[d][1,3]dioxol-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one(9i)



Docking Study:

Melanoma Derived Growth Regulatory Protein PDB ID: 1I1J

Protein name**: Melanoma derived growth regulatory protein,** Organisms(s): **Homo sapiens**,Sequence Length**=108,** Uniprot ID**: Q16674,** Gene Names:MIA

Grid data info:

Grid Point Spacing =1.000Angstroms**,**

Even Number of User-specified Grid Points =40-points 54y-points40z-points
Coordinates of Central Grid Point of Maps= (20.003, 21.173, 1.583)

Minimum coordinates in grid = (0.003, -5.827, -18.417)

Maximum coordinates in grid = (40.003, 48.173, 21.583)

Ligands used:

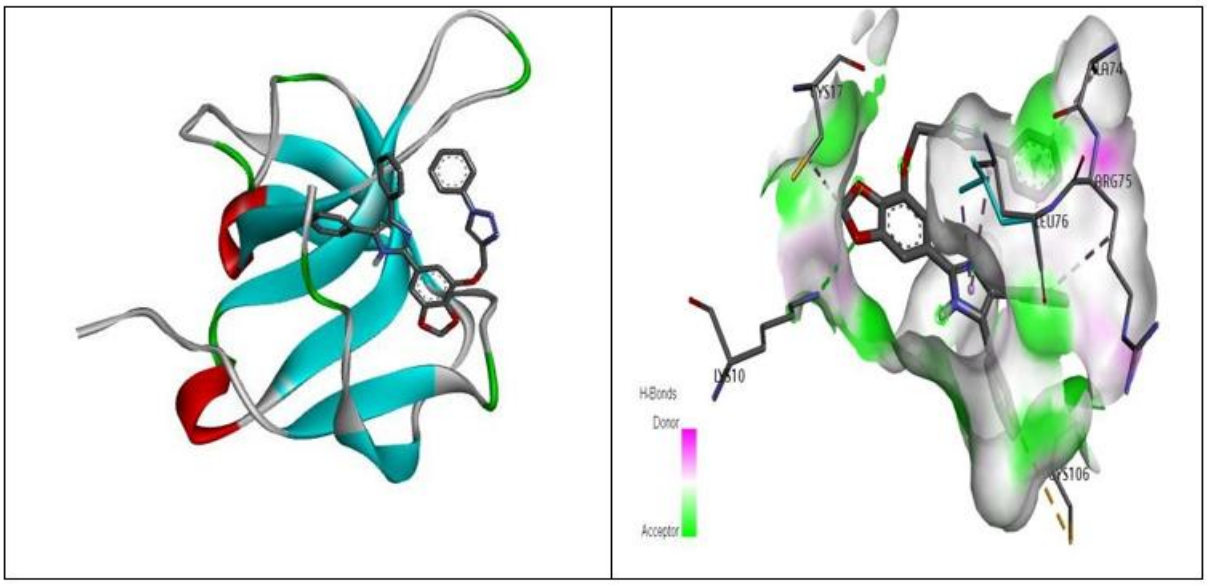
1) **Ligand name**: 7a**, Molecular Formula:** $C_{31}H_{2351}N_5O_3$, **Molecular Weight:** 513.000 .
2) **Ligand name**: 7b, **Molecular Formula:** $C_{31}H_{22}BrN_5O_3$**, Molecular Weight**: 592.44208
3) **Ligand name**: 7c, **Molecular Formula:** $C_{31}H_{22}ClN_5O_3$, **Molecular Weight**: 547.99108
4) **Ligand name**: 7d, **Molecular Formula:** $C_{31}H_{22}ClN_5O_3$, **Molecular Weight**: 547.99108
5) **Ligand name**: 7e, **Molecular Formula:** $C_{32}H_{25}N_5O_4$, **Molecular Weight**: 543.572
6) **Ligand name**: 7f, **Molecular Formula:** $C_{32}H_{25}N_5O_4$**, Molecular Weight**: 543.572
7) **Ligand name**: 7g, **Molecular Formula:** $C_{32}H_{25}N_5O_3$, **Molecular Weight**: 527.5726
8) **Ligand name**: 7h, **Molecular Formula:** $C_{32}H_{25}N_5O_3$, **Molecular Weight**: 527.5726

9) **Ligand name**: 7i, **Molecular Formula:** $C_{33}H_{25}N_5O_4$, **Molecular Weight**: 555.5827

10) **Ligand name**: 7j, **Molecular Formula:** $C_{31}H_{22}N_6O_5$, **Molecular Weight**: 558.54358

Lipinski's Rule information:

Sr. No.	Name of Co-former	Mol Weight (g/mol)	XLogP3	Hydrogen Bond Donor	HydrogenBond Acceptor	tatableBond
1	8a	527.5726	5.983601	0	7	152.417145
2	8b	606.46866	7.072593	0	6	158.532166
3	8c	562.01766	6.191571	0	6	152.911148
4	8d	562.01766	6.191571	0	6	152.911163
5	8e	557.59858	5.892801	0	8	157.988190
6.	8f	557.59858	6.318691	0	7	157.384186
7.	8g	541.59918	6.618512	0	6	155.569183
8.	8h	541.59918	6.618512	0	6	155.569183
9.	8i	569.60928	6.512692	0	7	160.836700
10	8j	572.57016	5.957191	0	8	156.507584



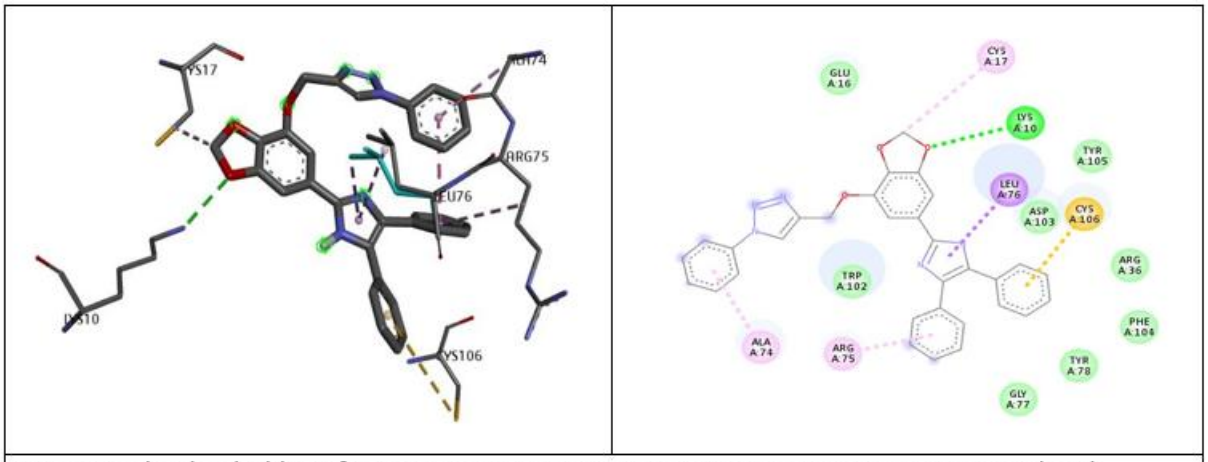


Figure Molecular docking of **Melanoma derived growth regulatory protein (1I1J)** Complexed with **8a** shows 3D model of the interactions and the 2D interaction patterns and H-bond interaction.

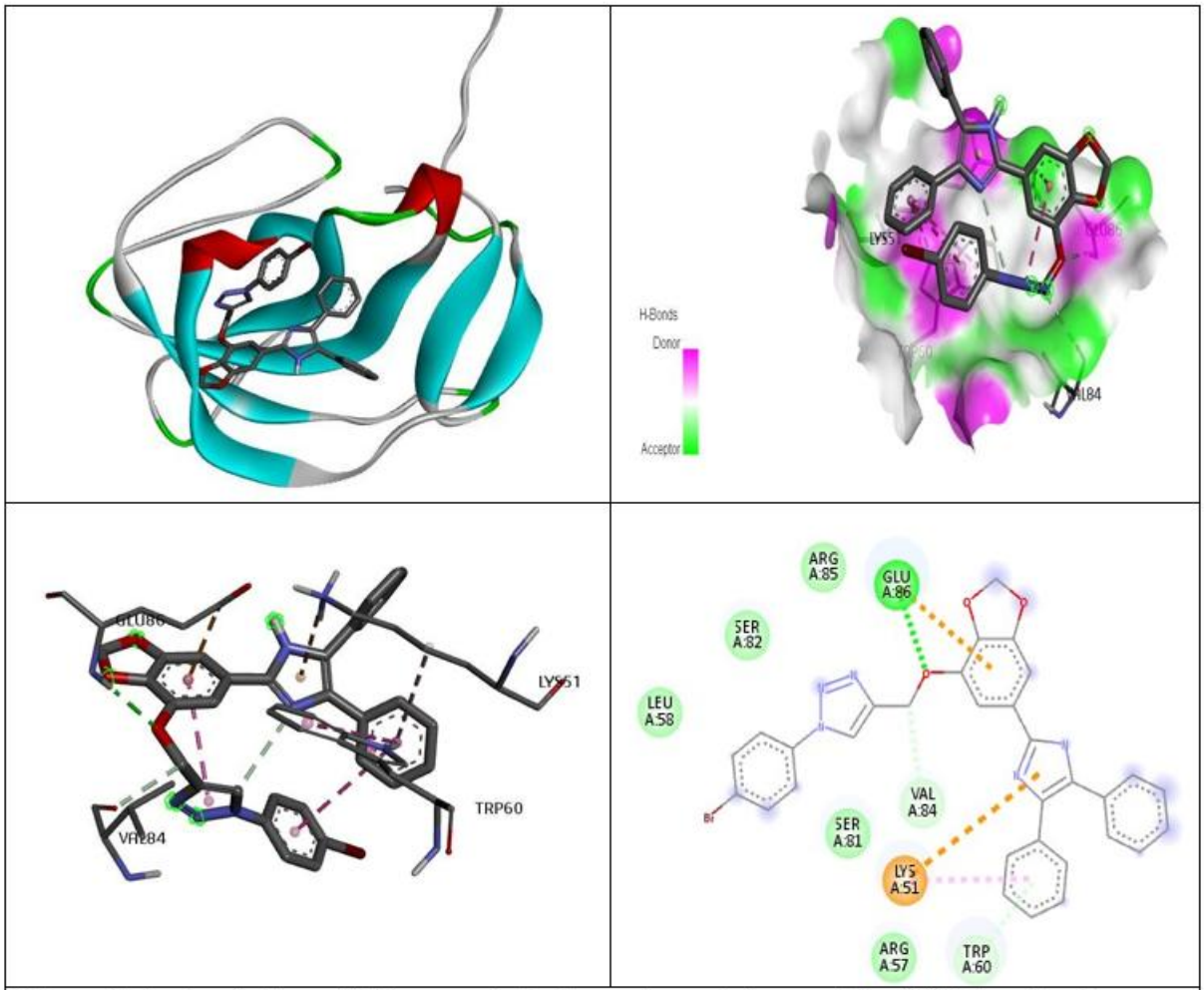


Figure Molecular docking of **Melanoma derived growth regulatory protein (1I1J)** Complexed with **8b** shows 3D model of the interactions and the 2D interaction patterns and H-bond interaction.

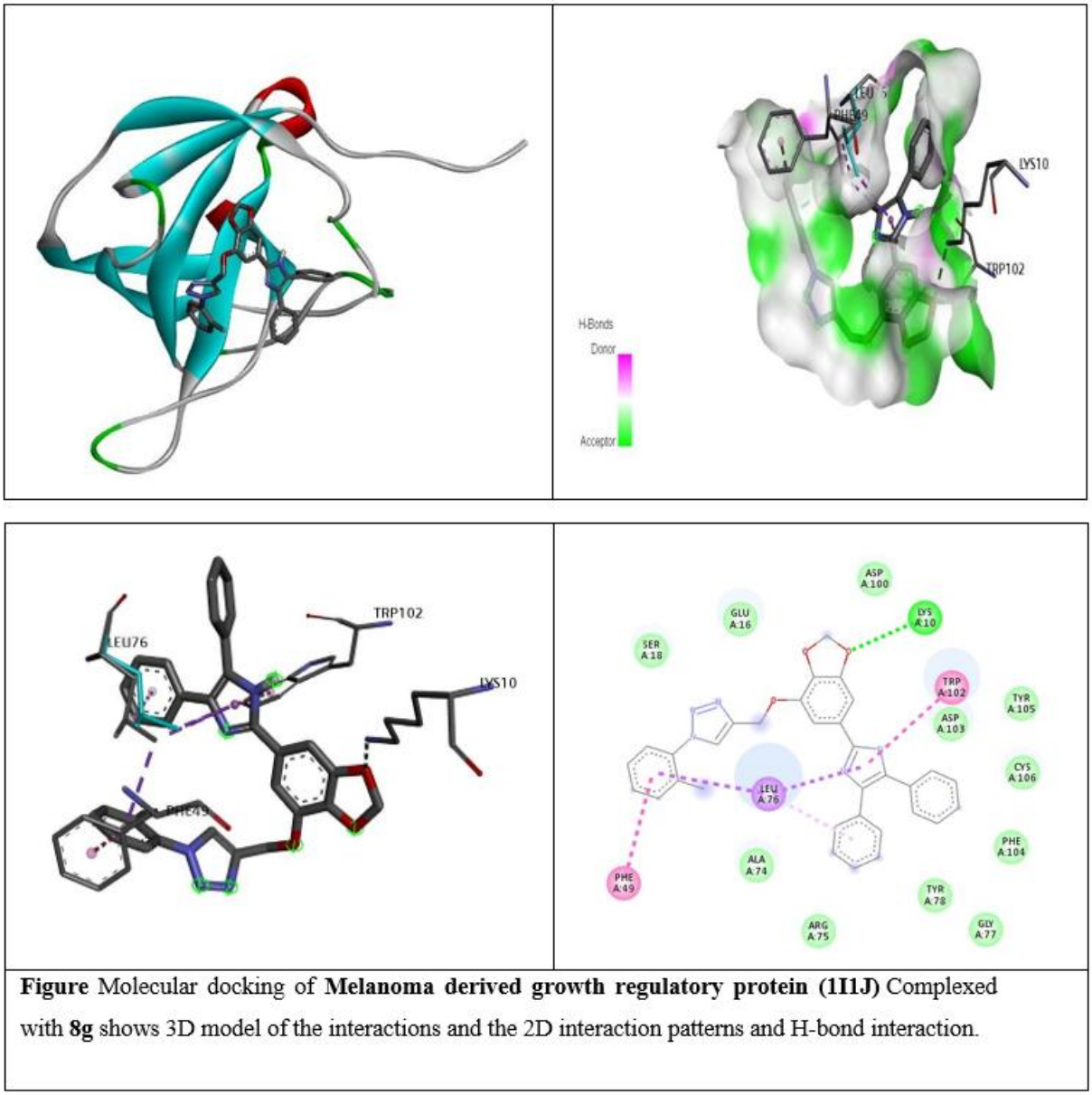


Figure Molecular docking of **Melanoma derived growth regulatory protein (1I1J)** Complexed with **8g** shows 3D model of the interactions and the 2D interaction patterns and H-bond interaction.

Ligand Preparation:

The 3-D structure of inhibitors were drawn in chemsketch and converted using the open babel converter and saved in PDB format. Furthermore, ligand preparations were continued by taking the 3-D structure of all the ligands and were introduced in Pymol software for conversion of 3-D structure from SDF to PDB format. Using Pymol software metals were also removed from the ligands structure for an appropriate docking study. The prepared ligands were saved in PDB format for further docking studies.

Protein preparation-

The crystal structure of Target proteins was retrieved from Protein Data Bank (PDB) with PDB ID **1I1J** and was carried further for more studies of docking process.

Molecular docking

Molecular Docking is an important component of computer-assisted drug discovery. It helps in predicting the intermolecular framework formed between a protein and ligand and outputs the appropriate binding between the molecules. Docking was performed by AutoDock 4.2.6 program, using the implemented empirical free energy function and the Lamarckian Genetic Algorithm (LGA). The grid maps were calculated using AutoGrid. In all dockings, a grid map with **40x 54 x 40**points and a grid-point spacing of **1.000Å** was applied.

The best conformation with the lowest docked energy was chosen from the docking search. The interactions of complex protein-ligand conformations including hydrogen bonds and bond lengths were analyzed using Pymol software, UCSF Chimera and Accelrys Discovery Studio Visualizer software.

3. DISCUSSION:

The best conformation with the lowest docked energy was chosen from the docking search. On performing the docking of the Melanoma derived growth regulatory protein (1I1J)with8a (- 8.20kcal/mol), 8b(-9.27kcal/mol),8c(-7.81kcal/mol), 8d(-8.72kcal/mol), 8e(-8.50kcal/mol), 8f(-8.26kcal/mol), 8g(-9.19kcal/mol), 8h(-9.15kcal/mol), 8i(-7.90kcal/mol), 8j(-7.93kcal/mol).it was observed that the binding energy shown by the protein and ligand is good at8b(-9.27kcal/mol). Number of torsions are choosen from 0-6, and if any ligand shows more than6 it is adjusted to 6. Hydrogen bond interactions are also calculated and mentioned, presence of H-bonds depicts stable interaction between ligand and protein. Discovery studio 2020 Client and Chimera softwares are used to depict Hydrogen bonds, 2-D images and protein-ligand interactions images for a good visualization of the docking. On performing the docking of the Protein name Melanoma derived growth regulatory protein (1I1J)8a (-8.20kcal/mol), 8b(-9.27kcal/mol),8c(-7.81kcal/mol), 8d(-8.72kcal/mol), 8e(-8.50kcal/mol), 8f(-8.26kcal/mol), 8g(-9.19kcal/mol), 8h(-9.15kcal/mol), 8i(-7.90kcal/mol), 8j(-7.93kcal/mol).It was observed that the binding energy shown by the protein and ligand is good.

Test Material: Synthetic compound Cell line used for testing sample: MCF-

Cell Culture and Maintenance:
The human breast cancer cells, MCF-7 were obtained from ATCC, USA. The cells were grown in MEM supplemented with 2mM L-glutamine, Sodium pyruvate (1mM/ml), MEM non- essential amino acids (1X), Insulin (5mg/ml), penicillin-streptomycin (100 U/ml) and 10% FBS.The cells were incubated in 5% CO_2 incubator at 37°C.

Method of Cell Viability Assay:
The effect of compounds on the viability of MCF-7 was determined by MTT dye assay. Thecells were seeded at a density of 1 x 105 cells/ml in 96-well plate and incubated at 37°C. Next day, the cells were dosed with different concentrations (0, 20, 40, 80, 160 and 320 µg/ml) of compounds compound a and compound b for 24h. The supernatant was removed and 100 µl MTT solution (5 mg/ml) was ided to each well. The plate was incubated at 37°C for 4 h to facilitate the formation of purple colored formazan crystals. The crystals were dissolved in 100µl of DMSO. After 15 min, the amount of colored formazan derivative was determined by measuring optical density (OD) at 570 nm and at reference filter 630nm by using FLUOstar omega multiplate reader, BMG labtech (Offenburg, Germany). The percentage viability was calculated as
% Viability = (OD of treated cells/OD of control cells) X 100

REFERENCES:

[1] E. K. Tiburu, M. Mutocheluh, P. K. Arthur, P. W. Narkwa, A. A. Salifu, M. A. Agyei, R. Yeboah, H. N. A. Fleischer, J. Zhuang, and G. Awandare, J. Biomater. Tissue Eng. 7, 544 (2017).

[2] A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman, CA Cancer J. Clin. 61, 69 (2011).

[3] Hussain Ali Almasmoum, Ghassan Almaimani, Riyad A. Almaimani, Abdullatif Taha Babakr, Maha Alsunbul, Hussah Abdullah Alshwyeh, Eman Serry Zayed, Ibrahim Abdel Aziz Ibrahim, & Essa M. Saied.

[4] Y. Draoui, S. Radi, Y. Bahjou, A. Idir, A. El Mahdaoui, A. Zyad, H. N. Miras, M. Ferbinteanu, A. Rotaru, Y. Garcia. *New triazole-based coordination complexes as antitumor agents against triple negative breast cancer MDA-MB-468 cell line*. *RSC Advances*, 2023, 13, 36158-36167.

[5] "Synthesis of New 1,2,3-Triazole-Based Compounds of Potential Anti-Breast Cancer Activity Targeting Aromatase Enzyme Inhibition." *Egyptian Journal of Chemistry*, 2023, Vol. 66, Issue 10, pp. 93-106.

[6] *Synthesis, Crystal Structure, Anticancer Evaluation and Hirshfeld Surface Analysis of Novel Antipyrine Gathered Bis-Triazoles as Breast Adenocarcinoma Inhibitors.* Journal of Structural Chemistry, 2024.

[7] Sarah A. Ghobish, Khaled O. Mohamed, Nahla Farag, Doaa B. Farag. "Novel indolyl 1,2,4-triazole derivatives as potential anti-proliferative agents: in silico studies, synthesis, and biological evaluation." RSC Medicinal Chemistry, 2024, 15, 293-308.

[8] "Design, Synthesis and Biological Evaluation of 1,2,4-Thiadiazole-1,2,4-Triazole Derivatives Bearing Amide Functionality as Anticancer Agents." Arabian Journal for Science & Engineering, 2020.

[9] *Development of di-arylated 1,2,4-triazole-based derivatives as therapeutic agents against breast cancer:*

synthesis and biological evaluation. RSC Medicinal Chemistry, 2024.
[10] *Synthesis and Anti-Breast Cancer Potency of Mono- and Bis-(pyrazolyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine) Derivatives as EGFR/CDK-2 Target Inhibitors.* ACS Omega, 2023.
[11] "Electrochemical Synthesis of New Isoxazoles and Triazoles Tethered with Thiouracil Base as Inhibitors of Histone Deacetylases in Human Breast Cancer Cells." *Molecules*, 2023, 28(13), 5254.
[12] "1,2,3-Triazole-Containing Hydrazones as Potential HER2 Kinase Inhibitors: Synthesis, Anticancer Evaluation, and Molecular Docking Study." *Russian Journal of Organic Chemistry*, 2024.
[13] "Triazole-tethered coumarin-indole fused chalcone-isatin derivatives as a new class of anti-breast cancer agents." *[Journal]*, *PubMed* 2023/2024 (JKUB2 with IC_{50} ~1.28 μM).
[14] G. L. Smith, Y. Xu, T. A. Buchholz, S. H. Giordano, J. Jiang, Y. C. Shih, and B. D. Smith, JAMA 307, 1827 (2012).
[15] D. Favia, O. Nicolotti, A. Stefanachi, F. Leonetti, and A. Carotti, Expert Opin. Drug Discov. 8, 395 (2013).
[16] M. A. C. Neves, T. C. P. Dinis, and G. Colombo, J. Med. Chem. 52, 143 (2009).
[17] J. Doiron, A. H. Soultan, R. Richard, M. M. Toure, N. Picot, R. Richard, C. M. Uperlovic, G.
[18] Robichaud, and M. Touaibia, Eur. J. Med. Chem. 46, 4010 (2011).
[19] H. Zhang, L. Zhao, C. Deng, N. Dong, and J. Shi, J. Biomater. Tissue Eng. 7, 735 (2017).
[20] S. Medjahed, S. Belaidi, S. Djekhaba, N. Tchouar, and A. Kerassa, J. Bionanosci. 10, 118 (2016).
[21] S. Khamouli, S. Belaidi, Z. Almi, S. Medjahed, and H. Belaidi, J. Bionanosci. 11, 301 (2017).
[22] F. Soualmia, S. Belaidi, H. Belaidi, N. Tchouar, and Z. Almi, J. Bionanosci. 11, 584 (2017).
[23] S. Nithiyanantham, L. Palaniappan, and M. Lenin, J. Bionanosci. 9, 359 (2015)