Pharmacogn. Res., 2025; 17(4):1281-1292.
https://www.phcogres.com

Original Article

Targeting Breast Cancer with Triazine Derivatives: A Molecular Docking Analysis of Her2 and Parp1 Inhibition

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ABSTRACT

Background: Heterocyclic compounds, particularly triazines, have significant attention in pharmaceutical and industrial research due to their broad spectrum of biological activities. **Objectives:** This study focuses on the synthesis and molecular docking analysis of 15 novel triazine derivatives (TCT1-TCT15) to evaluate their potential as inhibitors of two critical cancer-related targets: human epidermal growth factor receptor 2 (HER2) and poly (ADP-ribose) polymerase 1 (PARP1). **Materials and Methods:** The derivatives were synthesized by reacting 2,4,6-Trichloro-1,3,5-Triazine (TCT) with various aldehydes, thereby incorporating diverse substituent groups. Molecular docking was conducted using AutoDock 1.5.5, and protein-ligand interactions were visualized through Chimera software. **Results:** The docking results revealed strong binding affinities of the synthesized compounds to both HER2 and PARP1. For HER2, TCT9 (-12.73 kcal/mol), TCT4 (-12.47 kcal/mol), and TCT5 (-12.34 kcal/mol) showed the most favorable binding energies, all with inhibition constants in the nanomolar range. For PARP1, TCT13 (-13.96 kcal/mol), TCT12 (-13.64 kcal/mol), and TCT4 (-13.33 kcal/mol) demonstrated superior binding interactions, surpassing those of standard inhibitors. Structural analysis indicated that the presence of electron-withdrawing groups such as -Cl and -NO_2, as well as electron-donating groups like -OH and -OCH_3, significantly influenced the binding efficacy of the compounds. Stabilization of the protein-ligand complexes was primarily mediated by hydrogen bonding and hydrophobic interactions. **Conclusion:** These findings suggest that the synthesized triazine derivatives, particularly TCT9, TCT13, and TCT4, exhibit strong potential as anticancer agents, warranting further *in vitro* and *in vivo* investigations to explore their clinical applicability.

Keywords: Anticancer Activity, HER2, Molecular Docking, PARP1, S-Triazines, Triple-Negative Breast Cancer (TNBC).

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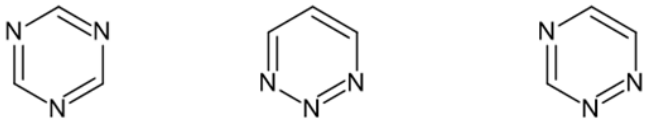
Received: 19-05-2025;
Revised: 01-07-2025;
Accepted: 29-08-2025.

INTRODUCTION

Heterocyclic compounds represent a significant class of organic molecules, comprising more than half of all known organic substances. These compounds are ubiquitous in a broad range of applications, including pharmaceuticals, vitamins, natural products, and various biologically active agents such as antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal substances.[1,2] Furthermore, heterocyclic compounds serve as essential building blocks in the development of synthetic drugs and agrochemicals.[3] Some of these compounds also exhibit intriguing properties such as solvatochromism, photochromism, and biochemical luminescence.[4] Beyond medicinal uses, they play a vital role in materials science, being utilized in dyes, fluorescent sensors, optical brighteners, data storage devices, plastics, and analytical reagents.[5] They are also valuable in the realms of supramolecular and polymer chemistry, particularly in the development of conjugated polymers.[6] For medicinal chemists, the core structures of heterocycles are particularly advantageous as they allow for the generation of a vast array of derivative compounds, which can be screened against various biological targets to identify multiple active agents.[7] The immense diversity of fused heterocyclic structures enables the creation of new polycyclic frameworks with diverse physical, chemical, and biological properties.[8] As a result, developing efficient synthetic methods to construct polycyclic scaffolds from biologically active heterocyclic templates remains a key goal for both organic and medicinal chemists.[9] Ultimately, the core

DOI: 10.5530/pres.20252332

aim of medicinal chemistry is to design and discover innovative therapeutic agents.[10]



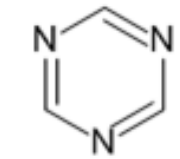
Isomeric forms of triazine (1), (2), and (3)

TRIAZINES

Nitrogen-containing heterocycles play a crucial role in both biological systems and industrial applications.[11] Among these, triazines are among the earliest discovered nitrogen heterocycles and consist of a six-membered ring incorporating three nitrogen atoms. Triazines exist in three isomeric forms: 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine.[12]

1,3,5 TRIAZINE

The symmetrical triazine ring system-commonly referred to as s-triazine-is also known as 1,3,5-triazine, a term often used in British scientific literature. The numbers in this name indicate where the nitrogen atoms are located within the six-membered ring.[13] Historically, older German texts referred to s-triazine as cyanide or γ-triazine, but today, the name s-triazine is widely accepted, especially in official chemical databases like Chemical Abstracts and the Ring Index.[14] In s-triazine, the nitrogen atoms occupy positions 1, 3, and 5, while the carbon atoms are at positions 2, 4, and 6. This arrangement gives the molecule a highly symmetrical structure, which contributes to its unique physical properties.[15] Physically, s-triazine is a crystalline solid known for its high volatility. It has a melting point of 86°C and a boiling point of 114°C at standard atmospheric pressure. It dissolves easily in ether (at around -5°C) and in ethanol.[16] The molecule's symmetrical nature explains its relatively high melting point and volatility. Due to this volatility, s-triazine can be easily removed from reaction mixtures by passing dry air or nitrogen over it a process known as entrainment.[17] The crystals themselves are highly refractive, rhombohedral in shape, and have a density of approximately 1.38 g/cm^3.[18] Interestingly,



adding nitrogen atoms to the ring doesn't significantly affect the boiling point, but it does cause a steady increase in the melting point.[19] In terms of practical use, s-triazine derivatives are widely applied in agriculture as herbicides-notably atrazine, simazine, and propazine.[20] In the pharmaceutical industry, s-triazines serve as intermediates in the production of antibacterial and antiviral drugs.[21] They also play a valuable role in polymer chemistry, particularly in the manufacture of fire retardants and cross-linking agents for resins.[22]

2,4,6-TRICHLORO-1,3,5-TRIAZINE

The chlorine atoms in 2,4,6-trichloro-1,3,5-triazine can be easily replaced by a variety of nucleophiles, especially when a hydrochloride acceptor-such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or a tertiary amine-is present. This reactivity makes it a valuable reagent for synthesizing mono-, di-, and tri-substituted 1,3,5-triazines.[23] The extent of chlorine substitution can be precisely controlled by adjusting the reaction temperature:

- Mono-substitution occurs at or below 0°C,[24]
- Di-substitution takes place around 40-45°C,[25]
- Tri-substitution requires temperatures above 120°C.[26]

However, substitution isn't solely dependent on temperature-it also varies with factors like the nucleophile's structure and basicity, steric hindrance, the nature of pre-existing substituents on the triazine ring, and the solvent used.[27] By carefully managing temperature, reaction time, solvent choice, and base selection, it's possible to replace the chlorine atoms in a one-pot reaction with different substituents, as long as the order of nucleophile addition is properly planned.[28] 2,4,6-Trichloro-1,3,5-triazine is an essential starting material for synthesizing cyanuric chloride derivatives, which are widely utilized in the production of reactive dyes, pharmaceutical compounds, and high-performance polymer materials.[29] Additionally, it is a key ingredient in the manufacturing of optical brighteners and UV stabilizers, expanding its significance across various industries.[30]

Pharmacological Actions of S-Triazines

S-triazines, a class of compounds featuring a six-membered ring with nitrogen atoms at the 1, 3, and 5 positions, exhibit a broad spectrum of pharmacological activities. Their diverse biological effects make them valuable in multiple therapeutic areas.[31] Here are some of their notable activities:

- **Antimicrobial Activity:** S-triazines demonstrate strong antibacterial, antifungal, and antiviral properties. Their antimicrobial efficacy is largely attributed to their ability to interfere with DNA replication and inhibit microbial growth.[32]

- **Anticancer Activity:** Certain S-triazine compounds have shown potential in cancer therapy by inducing apoptosis (programmed cell death), causing cell cycle arrest, and suppressing tumor cell proliferation.[33]
- **Anti-inflammatory Activity:** Some S-triazine derivatives exert anti-inflammatory effects by modulating pro-inflammatory cytokines and other mediators involved in inflammation.[34]
- **Antioxidant Activity:** These compounds also have potential antioxidant properties, helping to reduce oxidative stress and protect cells from damage caused by free radicals.[35]
- **Enzyme Inhibition:** Certain derivatives act as enzyme inhibitors, notably of acetylcholinesterase, an enzyme linked to neurodegenerative diseases such as Alzheimer's, making them promising candidates for neurological drug development.[36]

2,4,6-Trichloro-1,3,5-Triazine (TCT)

2,4,6-Trichloro-1,3,5-Triazine (TCT) is a chlorinated derivative of s-triazine widely utilized in both industrial and pharmaceutical fields. It serves as a versatile building block in the synthesis of agrochemicals, herbicides, and is frequently used as a reagent in various chemical processes.[37] Here are some of the notable activities and applications of TCT and its derivatives

- **Herbicidal Action:** TCT-based compounds are extensively used in agriculture due to their strong herbicidal properties. They work by inhibiting photosynthesis in plants, effectively controlling weed growth.[38]
- **Antiviral Activity:** Research indicates that certain TCT derivatives have antiviral effects, functioning by disrupting viral replication, making them potential candidates for antiviral drug development.[39]
- **Insecticidal Activity:** Some derivatives of TCT exhibit insecticidal properties, targeting the nervous system of insects and pests, which makes them useful in pest control applications.[40]
- **Potential Anticancer Activity:** TCT derivatives are also being explored for their anticancer potential. They may act through mechanisms such as inducing apoptosis (cell death) and inhibiting cancer cell proliferation.[41]

Due to this wide range of bioactivities, TCT remains a valuable compound in the development of pharmaceuticals, pesticides, and other specialty chemicals.[42]

Cancer

Cancer is a complex group of diseases marked by uncontrolled cell growth and the potential to spread to other parts of the body, arising from genetic mutations and abnormal gene expression. It can originate in nearly any tissue, forming solid tumors or affecting the blood and lymphatic systems, as seen in leukemia and lymphoma.[43] The most common types include carcinomas (e.g., breast, lung, colorectal), sarcomas (e.g., bone, fat), and hematologic cancers (e.g., leukemia, lymphoma, multiple myeloma).[44] While inherited genetic mutations account for only 5-10% of cases, environmental exposures (radiation, pollution, toxins) and lifestyle factors (smoking, alcohol, poor diet, stress, inactivity) play significant roles.[45] Aging also increases cancer risk, as does DNA damage from carcinogens and infections.[46] Although not all tumors are malignant, cancerous tumors can invade nearby tissues and metastasize.[47] According to the WHO, cancer is the second leading cause of death worldwide, with men most commonly diagnosed with lung, prostate, and colorectal cancers, while women frequently develop breast, colorectal, and lung cancers.[48] In children, leukemia, brain tumors, and lymphoma are most prevalent.[49] Diagnosis and treatment rely on early detection and targeted therapies; breast cancer, for example, is classified by markers like the Estrogen Receptor (ER) and HER2, which influence treatment decisions.[50] Standard treatments include surgery, chemotherapy, radiation, immunotherapy, and hormone therapy,[51] though these often cause serious side effects such as fatigue, immune suppression, and organ-specific toxicities (e.g., cardiotoxicity from anthracyclines, pulmonary toxicity from bleomycin).[52] As conventional methods face challenges like toxicity and resistance, innovations like nanotechnology are being explored to improve diagnostic accuracy and therapeutic outcomes, especially as cancer cases continue to rise, with 1.9 million new diagnoses estimated by the end of 2021.[53]

Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women.[54] While many cases are benign and manageable through surgical intervention, approximately 25% exhibit a slow-growing yet aggressive nature that facilitates early metastasis.[55] Although current therapies can delay tumor progression, recurrence is common, contributing to high mortality rates.[56] The behavior of breast cancer cells is rooted in the early developmental stages of embryonic mammary cells, which are inherently motile and invasive-traits essential for normal development but also critical in cancer spread.[57] Carcinogenesis, the process by which normal cells transform into cancerous ones, is characterized by six hallmarks: evading apoptosis, limitless replication potential, enhanced angiogenesis, resistance to growth-inhibitory signals, promotion of growth signals, and the capacity to metastasize.[58] These changes are driven by genetic and environmental factors.[59] With cancer emerging as a major global health challenge, it significantly diminishes quality of life and results in high treatment

costs, even if not always fatal.[60] Breast cancer alone accounts for 2.3 million new cases globally according to GLOBOCAN 2020 and ranks as the fifth leading cause of cancer-related deaths.[61] Mortality is higher in transitioning regions such as Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean compared to more developed areas like Australia/New Zealand, Western Europe, North America, and Northern Europe.[62] Prevention and early detection through behavioral changes and screening programs are essential for reducing breast cancer rates.[63] Organizations like the Breast Health Global Initiative (BHGI) are instrumental in developing international guidelines for breast cancer management.[64] This review specifically addresses breast cancer in women, as it remains the most prevalent form of cancer among females.[65]

Types of Breast Cancer

- **Non-Invasive Breast Cancer:** In this type, cancerous cells remain confined within the milk ducts, without breaching the surrounding fatty or connective tissues. Ductal Carcinoma *in situ* (DCIS) is the most prevalent form, representing about 90% of non-invasive breast cancer cases.[66] Lobular Carcinoma *in situ* (LCIS), though less common, serves as an indicator of elevated breast cancer risk.[67]
- **Invasive Breast Cancer:** This category involves malignant cells penetrating the duct or lobular walls, allowing them to infiltrate adjacent breast tissue. However, not all invasive cancers immediately spread (metastasize) to lymph nodes or other body organs.[68]
- **Triple-Negative Breast Cancer (TNBC):** Representing approximately 10-15% of breast cancer cases, TNBC is defined by the absence of estrogen, progesterone, and HER2 receptors on tumor cells.[69] This subtype is more frequently diagnosed in women under 40, particularly those of African descent or carrying the BRCA1 gene mutation.[70] TNBC often aligns with the basal-like molecular classification and typically does not respond to HER2-directed treatments.[71]

POLY (ADP-RIBOSE) POLYMERASE (PARP1)

PARP1 is an enzyme from a family that facilitates the transfer of ADP-ribose units to proteins, playing a crucial role in cellular processes such as transcription regulation, chromatin remodeling, DNA replication, recombination, and especially in DNA repair.[72] PARP enzymes are significant in cancer therapy development because of their involvement in DNA damage repair. Blocking PARP1 activity compromises this repair mechanism, making cancer cells more susceptible to treatments that induce DNA damage, like chemotherapy and radiation.[73] Thus, PARP1 inhibitors enhance the efficacy of these therapies.[74] In several cancer types, PARP1 is a key DNA repair pathway, and its inhibition results in genomic instability and cell death.[75] Additionally, tumor suppressor genes such as BRCA1 and BRCA2, which are vital for double-strand DNA break repair through homologous recombination, work in conjunction with PARP1.[76] Disrupting both BRCA and PARP1 functions leads to an accumulation of DNA damage in cancer cells, ultimately causing cell death, which highlights the therapeutic value of this dual inhibition strategy (Figure 1).[77]

HER 2

HER2 is a receptor protein that is homologous to oncogenic growth factor receptors found in humans and rodents. It was initially discovered as an amplified gene in human breast cancer cells and was named HER2.[78] HER2 shares structural similarities with the Epidermal Growth Factor Receptor (EGFR) and has intrinsic tyrosine kinase activity.[79] Proteins in the HER family are classified as type I transmembrane growth factor receptors and are essential for initiating intracellular signaling in response to external signals.[80] These receptors consist of three primary regions: an extracellular domain for ligand binding, a transmembrane region, and an intracellular domain with tyrosine kinase activity.[81] Upon ligand binding, HER family receptors dimerize and undergo transphosphorylation, which activates downstream signaling pathways that govern cell proliferation and survival.[82] Detailed genetic analysis and post-genomic studies have led to the identification of four receptor family members: EGFR (HER1/erbB1), HER2 (erbB2/HER2/neu), HER3 (erbB3), and HER4 (erbB4) (Figure 2).[83]

Molecular Docking

Molecular docking is a computational method used to simulate the interaction between a ligand (a small molecule) and a target macromolecule such as a protein, DNA, or RNA. It is extensively applied in drug discovery, structural biology, and studies of enzyme-ligand interactions, aiming to identify potential therapeutic compounds and refine lead candidates.[84] The central objective of molecular docking is to predict the optimal binding conformation of a ligand within the receptor's active site and assess the strength of this interaction.[85] The docking process involves two primary steps: predicting the ligand's binding orientation (pose prediction) and estimating the binding strength (binding affinity), which is evaluated through scoring functions.[86] These functions consider hydrogen bonds, hydrophobic interactions, and electrostatic forces.[87] Docking algorithms explore a range of ligand conformations to identify the most stable interaction.[88] There are two main types of docking:

- Rigid docking assumes fixed structures for both ligand and receptor, allowing only positional adjustments.[89]
- Flexible docking permits conformational changes in either the ligand, the receptor, or both, thereby

providing a more accurate representation of biological interactions.[90]

Molecular docking is foundational in Structure-Based Drug Design (SBDD), enabling high-throughput screening of compound libraries for inhibitory potential.[91] However, its precision depends on variables like protein flexibility, solvent effects, and the accuracy of scoring methods.[92] To improve reliability, docking results are often validated with molecular dynamics simulations and experimental data.[93] Despite inherent challenges, docking remains an essential tool in computational drug discovery and biomedical research.[94]

AutoDock 1.5.5

AutoDock 1.5.5 is a widely used molecular docking software developed by The Scripps Research Institute, designed to predict interactions between small molecules (ligands) and large biomolecular targets, including proteins, DNA, and RNA.[95] It is part of the AutoDock suite, which also includes AutoGrid for preparing the grid maps essential for docking calculations.[96] AutoDock 1.5.5 supports both rigid and flexible docking approaches, making it adaptable for studying diverse molecular interactions such as protein-ligand, protein-protein, and nucleic acid-ligand bindings.[97] It employs search algorithms like the Lamarckian Genetic Algorithm (LGA) and Simulated Annealing

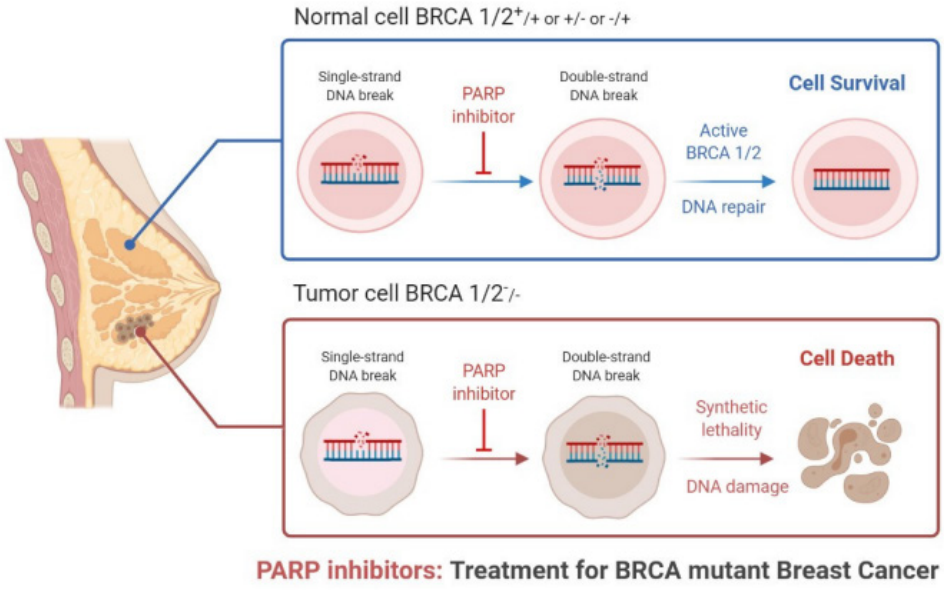


Figure 1: POLY (ADP-RIBOSE) POLYMERASE (PARP1).

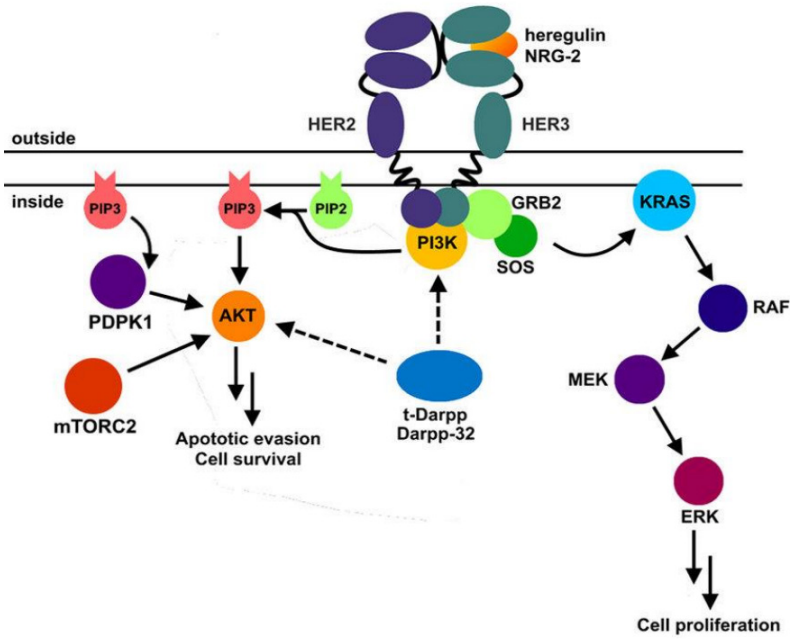


Figure 2: Human Epidermal Receptor.

to examine different ligand orientations and determine the most energetically favorable binding poses.

MATERIALS AND METHODS

Protein Preparation

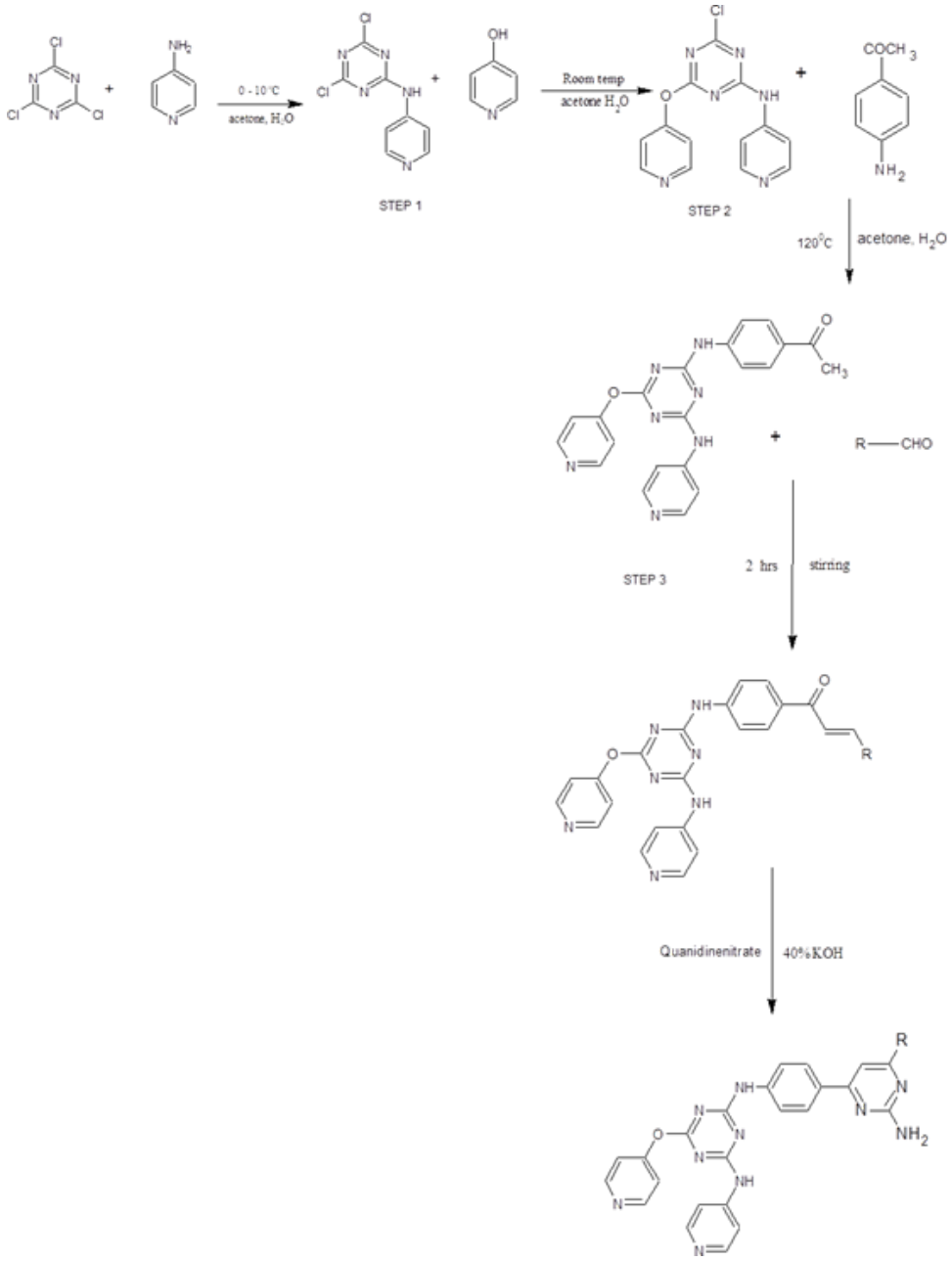
The three-dimensional structures of HER2 (PDB ID: 8U8X) and PARP1 (PDB ID: 7KK4) were obtained from the RCSB Protein Data Bank. These structures were processed using AutoDock Tools 1.5.5 to prepare them for molecular docking. Preparation included removing water molecules, adding polar hydrogens, assigning Kollman partial charges, and applying AD4 atom types. The structures were saved in the.pdbqt file format, ensuring readiness for docking simulations.

Ligand Preparation

Fifteen ligands (TCT1 to TCT15) were initially drawn in 2D using Marvin Sketch and then converted to 3D using Marvin View for spatial optimization. These structures were saved in. PDB format and subsequently processed in Auto Dock Tools 1.5.7, where they were converted to.pdbqt format for docking.

Molecular Docking Analysis

Docking simulations were performed using Auto Dock 1.5.5. Each ligand underwent twenty-five independent docking runs for accurate binding predictions. The simulations used specific grid box parameters (Table 1), and results were analyzed for binding energy and inhibition constants to assess interaction strength and stability.



Protein-Ligand Complex Visualization

Chimera software was used to visualize the resulting protein-ligand complexes. This allowed for detailed analysis of hydrophobic and polar interactions. Both 2D and 3D images of these interactions were created to deepen the understanding of the docking mechanisms.

Scheme for the synthesis of designed derivatives

Where R(aldehyde)substituted in

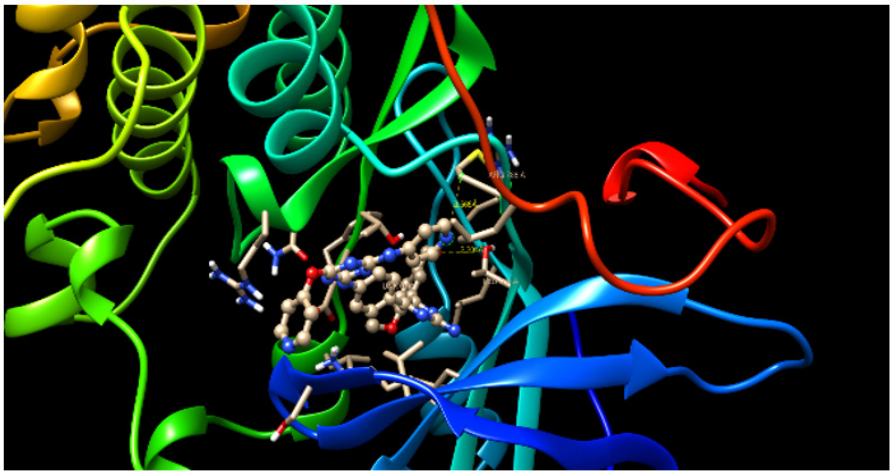
1. TCT1 is Benzaldehyde,
2. TCT2 is 4-Hydroxy benzaldehyde,
3. TCT3 is 4-methoxy benzaldehyde,
4. TCT4 is 4-chloro benzaldehyde,
5. TCT5 is 2-hydroxy benzaldehyde,
6. TCT6 is furfural,
7. TCT7 is Thiophene 2 carbaldehyde,
8. TCT8 is pyridine-2-carbaldehyde,
9. TCT9 is cinnamaldehyde,
10. TCT10 is hexanal,
11. TCT 11 is 2- methyl pentanal,
12. TCT12 is 3,4-Dihydroxy benzaldehyde,
13. TCT13 is 4-nitro benzaldehyde,
14. TCT14 is 5-hydroxy-2-methoxy benzaldehyde,
15. TCT15 is perilialdehyde.

RESULTS

Molecular Docking Docking simulations assessed interactions between TCT1-TCT15 ligands and target proteins HER2 (PDB ID: 8U8X) and PARP1 (PDB ID: 7KK4). Binding energy, ligand efficiency, inhibition constants, and interaction energy were analyzed. HER2 docking scores indicated that most designed compounds bound more effectively than the reference standard. TCT9 (-12.73 kcal/mol), TCT4 (-12.47 kcal/mol), TCT5 (-12.34 kcal/mol), and TCT12 (-12.56 kcal/mol) exhibited strong HER2 binding. TCT9 demonstrated the best binding energy and a low inhibition constant of 464.9 nM. TCT4 and TCT5 also performed well with constants of 718.83 nM and 900.69 nM, respectively. The reference compound (-10.84 kcal/mol) showed weaker binding. Van der Waals, hydrogen bonding, and desolvation energy contributed to the stability of TCT9, TCT4, and TCT5 interactions with HER2, mainly through hydrophobic and hydrogen bonding interactions. PARP1 docking results also revealed superior binding energies for several compounds compared to the reference. TCT13 (-13.96 kcal/mol), TCT12 (-13.64 kcal/mol), TCT4 (-13.33 kcal/mol), TCT15 (-13.41 kcal/mol), and TCT2 (-13.12 kcal/mol) were top performers. TCT13 showed the best binding and a low inhibition constant of 58.09

Table 1: Energy Minimization Table for HER2 (PDB ID-8U8X) (Figure 3).

Compound code	Binding energy	Ligand efficiency	Inhibitory constant	Vdw-hb-desolvation energy	Intermol energy
TCT1	-11.93	-0.28	1.79	-14.26	-14.62
TCT2	-11.88	-0.28	1.95	-14.12	-14.57
TCT3	-11.7	-0.27	2.67	-14.31	-14.68
TCT4	-12.47	-0.29	718.83	-14.69	-15.16
TCT5	-12.34	-0.29	900.69	-14.69	-15.02
TCT6	-11.29	-0.28	5.28	-13.25	-13.68
TCT7	-11.79	-0.29	2.28	-13.74	-14.18
TCT8	-11.65	-0.28	2.87	-13.69	-14.34
TCT9	-12.73	-0.29	464.9	-15.37	-15.71
TCT10	-10.59	-0.26	17.31	-14.18	-14.47
TCT11	-10.9	-0.27	10.27	-14.08	-14.48
TCT12	-12.56	-0.29	617.62	-14.86	-15.25
TCT13	-12.05	-0.26	1.48	-14.56	-15.03
TCT14	-12.46	-0.28	735.25	-14.83	-15.15
TCT15	-11.99	-0.27	1.64	-14.52	-14.97
Standard	-10.84	-0.34	11.29	-12.05	-12.04



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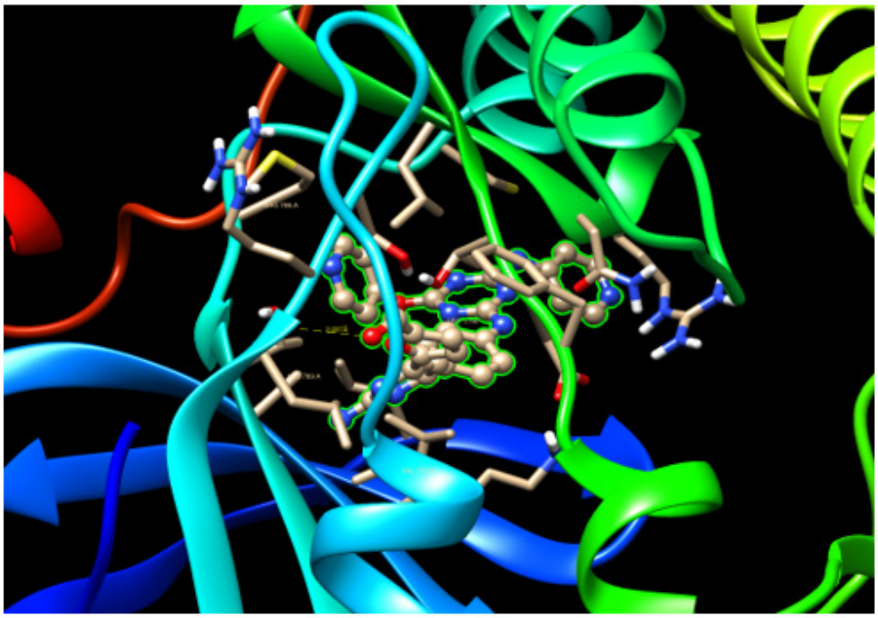

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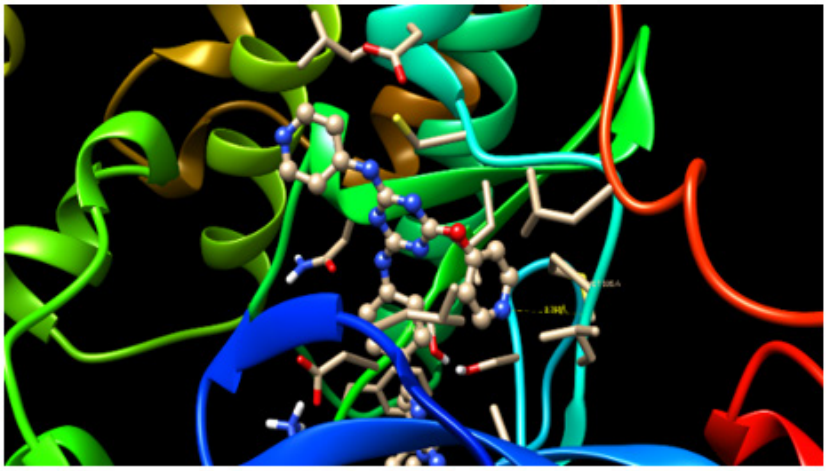

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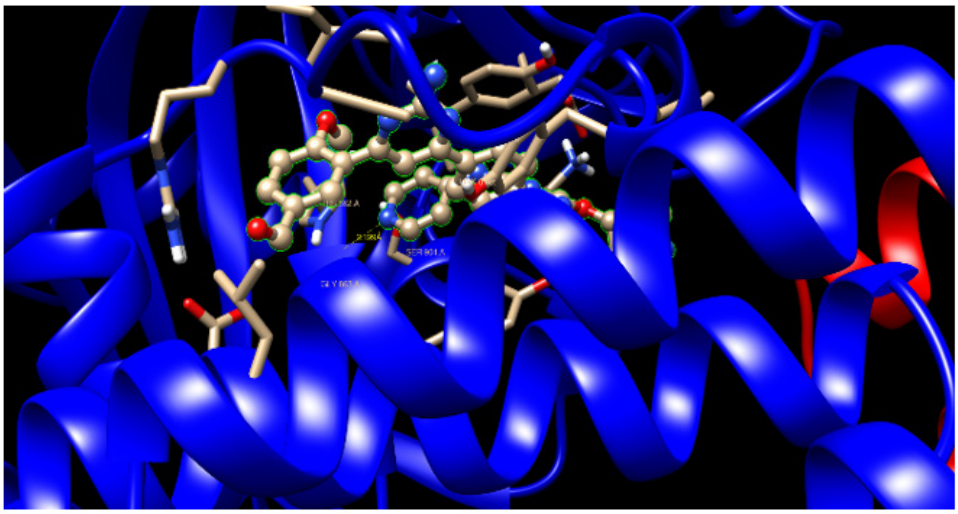
Figure 3: HER2(PDB ID-8U8X) A-TCT 4,B-TCT9,C-TCT13.



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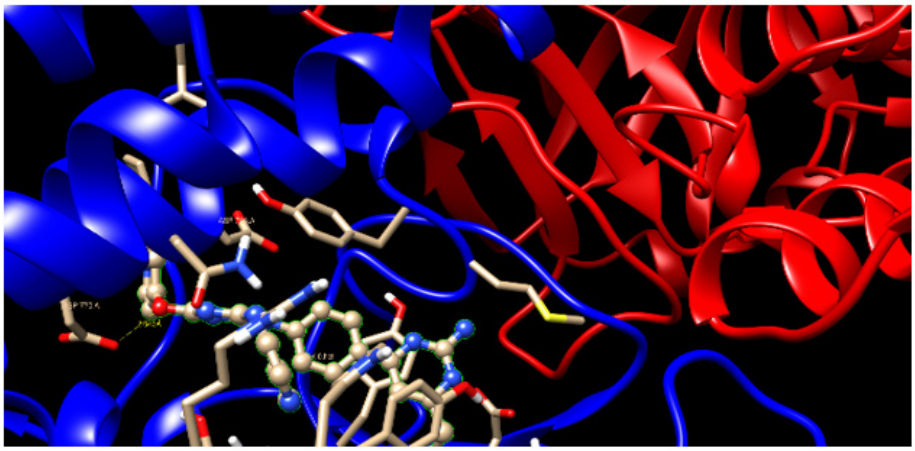

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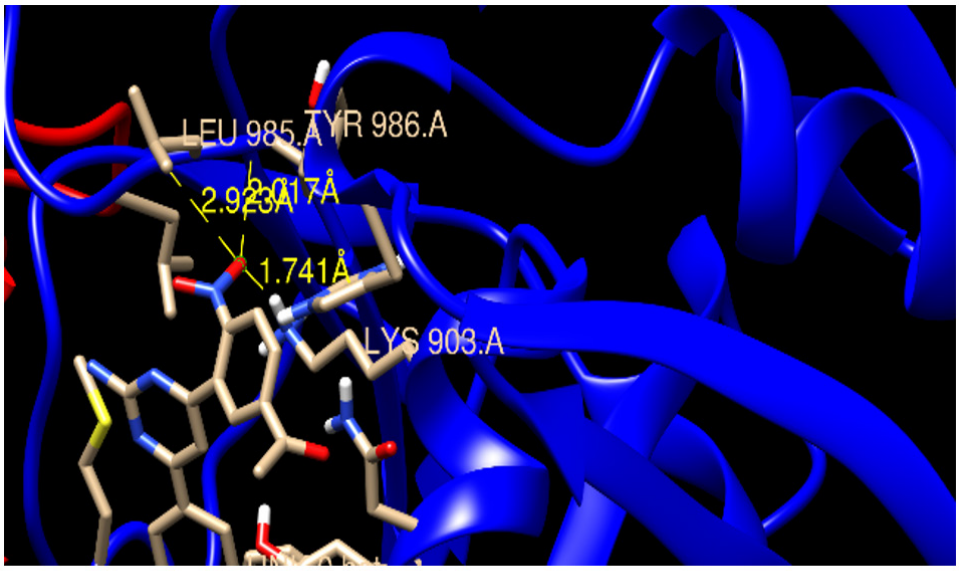

(C)

Figure 4: PARP1(PDB ID:7KK4) A-TCT 4,B-TCT12,C-TCT13.

Table 2: Energy Minimization Table for PARP1 (PDB ID:7KK4) (Figure 4).

Compound code	Binding energy	Ligand efficiency	Inhibitory constant	Vdw-hb-desolvation energy	Intermol energy
TCT1	-12.8	-0.3	414.71	-14.47	-15.48
TCT2	-13.12	-0.31	242.26	-13.64	-15.8
TCT3	-12.64	-0.29	547.41	-14.71	-15.62
TCT4	-13.33	-0.31	170.54	-15.34	-16.01
TCT5	-12.06	-0.28	1.45	-14.01	-14.74
TCT6	-11.83	-0.29	2.14	-12.03	-14.21
TCT7	-12.72	-0.31	472.21	-14.17	-15.11
TCT8	-11.83	-0.28	2.12	-13.7	-14.52
TCT9	-12.22	-0.28	1.11	-14.64	-15.2
TCT10	-11.94	-0.29	1.78	-14.04	-15.82
TCT11	-11.69	-0.29	2.69	-13.73	-15.27
TCT12	-13.64	-0.31	101.02	-15.64	-16.32
TCT13	-13.96	-0.3	58.09	-14.66	-16.95
TCT14	-12.83	-029	395.34	-14.4	-15.51
TCT15	-13.41	-0.3	146.88	-15.52	-16.4
Standard	-10.62	-027	16.35	-13.23	13.9

nM, while TCT12 and TCT4 followed closely. The reference compound (-10.62 kcal/mol) was less effective. Comparative analysis highlighted TCT4, TCT12, and TCT13 as strong binders for both targets. TCT9 was optimal for HER2, while TCT13 led for PARP1. Overall, the designed compounds had higher binding energies than the standard, indicating strong inhibitory potential. Chimera visualization identified key stabilizing interactions. TCT9 and TCT4 formed multiple hydrogen bonds with HER2, while TCT13 and TCT12 exhibited hydrogen bonding and π-π stacking with PARP1. Hydrophobic interactions further stabilized the complexes. Structure-activity relationship analysis indicated that electron-withdrawing (-Cl, -NO_2) and electron-donating (-OH, -OCH_3) groups influenced binding strength. Electron-withdrawing groups enhanced binding scores, while hydroxyl and methoxy groups contributed through hydrogen bonding.

CONCLUSION

In this study, fifteen novel triazine derivatives (TCT1-TCT15) were synthesized and evaluated for their potential as inhibitors of HER2 and PARP1, two critical proteins implicated in cancer progression. Molecular docking studies using AutoDock 1.5.5 revealed that several of these compounds exhibited strong binding affinities to both HER2 and PARP1, surpassing the reference standards in terms of binding energy and inhibition constants. Notably, TCT9, TCT4, and TCT5 demonstrated exceptional binding to HER2, with TCT9 showing the highest binding energy (-12.73 kcal/mol) and a low inhibition constant of 464.9 nM. For PARP1, TCT13, TCT12, and TCT4 emerged as the most potent inhibitors, with TCT13 exhibiting the strongest binding affinity (-13.96 kcal/mol) and an inhibition constant of 58.09 nM. The structural analysis highlighted the importance of electron-withdrawing groups (-Cl, -NO_2) and electron-donating groups (-OH, -OCH_3) in enhancing binding efficacy. Hydrogen bonding, hydrophobic interactions, and π-π stacking were identified as key stabilizing forces in the protein-ligand complexes. These findings underscore the potential of the synthesized triazine derivatives as promising anticancer agents targeting HER2 and PARP1. Overall, this research provides valuable insights into the design and development of novel triazine-based inhibitors with enhanced therapeutic potential. The results call for further *in vitro* and *in vivo* studies to validate the efficacy and safety of these compounds, paving the way for their potential application in cancer therapy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TCT: Trichloro triazene; **HER:** Human Epidermal receptor; **PARP1:** POLY (ADP-RIBOSE) POLYMERASE (PARP1); **DNA:** Deoxy ribo neuclic acid; **RNA:** Ribo neuclic acid; **PDB:** Protien Data bank; **TNBC:** Triple-Negative Breast Cancer; **WHO:** World Health Organiztion.

SUMMARY

This research presents the design, synthesis, and molecular docking analysis of fifteen novel 1,3,5-triazine derivatives (TCT1-TCT15) aimed at inhibiting two critical breast cancer targets: HER2 and PARP1. Using AutoDock 1.5.5, the study evaluated the binding affinities and inhibition constants of these compounds, identifying several derivatives with superior docking performance compared to standard inhibitors. Notably, TCT9 showed the strongest binding to HER2 (-12.73 kcal/mol, Ki = 464.9 nM), while TCT13 was the most potent against PARP1 (-13.96 kcal/mol, Ki = 58.09 nM). Structural insights revealed that electron-withdrawing (e.g., -Cl, -NO_2) and electron-donating groups (e.g., -OH, -OCH_3) significantly contributed to binding strength through hydrogen bonding, hydrophobic interactions, and π-π stacking. These findings highlight the potential of triazine scaffolds as dual-target inhibitors for HER2 and PARP1 and support their further evaluation through biological studies for future anticancer therapy development.

REFERENCES

1. Alvarez-Builla J, Vaquero JJ, Barluenga J, editors. Modern heterocyclic chemistry. John Wiley & Sons; 2011. doi: 10.1002/9783527637737.
2. Almulla AF. Pharma D, Al-Mulla A.A review: biological importance of heterocyclic compounds. Pharm Chem. 2017; 9.
3. Qadir T, Amin A, Sharma PK, Jeelani I, Abe H. A review on medicinally important heterocyclic compounds. Open Med Chem J. 2022; 16(1). doi: 10.2174/18741045-v16-e2202280.
4. Kidwai M, Venkataramanan R, Mohan R, Sapra P. Cancer chemotherapy and heterocyclic compounds. Curr Med Chem. 2002; 9(12): 1209-28. doi: 10.2174/0929867023370059, PMID 12052173.
5. Giacomelli G, Porcheddu A, Luca L. [1,3,5]-triazine: A versatile heterocycle in current applications of organic chemistry. Curr Org Chem. 2004; 8(15): 1497-519. doi: 10.2174/1385272043369845.
6. Ali MI, Naseer MM. Recent biological applications of heterocyclic hybrids containing s-triazine scaffold. RSC Adv. 2023; 13(43): 30462-90. doi: 10.1039/d3ra05953g, PMID 37854486.
7. Gamez P, Reedijk J. 1,3,5-triazine-based synthons in supramolecular chemistry. Eur J Inorg Chem. 2006; 2006(1): 29-42. doi: 10.1002/ejic.200500672.
8. Case FH, Koft E. The synthesis of certain substituted 1,3,5-triazines containing the ferroin group. J Am Chem Soc. 1959; 81(4): 905-6. doi: 10.1021/ja01513a037.
9. Menicagli R, Malanga C, Peluso P. Selective mono- or dialkoxylation of 2,4,6-trichloro-1,3,5-triazine in solid-liquid phase transfer conditions. Synth Commun. 1994; 24(15): 2153-8. doi: 10.1080/00397919408010229.
10. Blotny G. Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. ChemInform. 2006; 37(51). doi: 10.1002/chin.200651255.
11. Zacharie B, Abbott SD, Duceppe JS, Gagnon L, Grouix B, Geerts L, *et al.* Design and synthesis of new 1,3,5-trisubstituted triazines for the treatment of cancer and inflammation. ChemistryOpen. 2018; 7(9): 737-49. doi: 10.1002/open.201800136, PMID 30258746.
12. Blotny G. Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. Tetrahedron. 2006; 62(41): 9507-22. doi: 10.1016/j.tet.2006.07.039.
13. Sheyi R, Mhlongo JT, Jorba M, Fusté E, Sharma A, Viñas M, *et al.* 1,3,5-triazine as branching connector for the construction of novel antimicrobial peptide dendrimers: synthesis and biological characterization. Int J Mol Sci. 2024; 25(11): 5883. doi: 10.3390/ijms25115883, PMID 38892071.
14. Srinivas K, Srinivas U, Bhanuprakash K, Harakishore K, Murthy US, Rao VJ. Synthesis and antibacterial activity of various substituted s-triazines. Eur J Med Chem. 2006; 41(11): 1240-6. doi: 10.1016/j.ejmech.2006.05.013, PMID 16815597.
15. Dai Q, Sun Q, Ouyang X, Liu J, Jin L, Liu A, *et al.* Antitumor activity of s-triazine derivatives: A systematic review. Molecules. 2023; 28(11): 4278. doi: 10.3390/molecules28114278, PMID 37298753.
16. Marín-Ocampo L, Veloza LA, Abonia R, Sepúlveda-Arias JC. Anti-inflammatory activity of triazine derivatives: A systematic review. Eur J Med Chem. 2019; 162: 435-47. doi: 10.1016/j.ejmech.2018.11.027, PMID 30469039.
17. Shukla V, Pathak M, Mishra GP, Pandey RK. Pharmacological activities of hybrid derivatives of s-triazine: a review. Int J Pharmacognosy Pharm Sci. 2019; 1(1): 42-9. doi: 10.33545/27067009.2019.v1.i1a.82.
18. He H, Liu Y, You S, Liu J, Xiao H, Tu Z. A review on recent treatment technology for herbicide atrazine in contaminated environment. Int J Environ Res Public Health. 2019; 16(24): 5129. doi: 10.3390/ijerph16245129, PMID 31888127.
19. Sumoto K, Mibu N, Yokomizo K, Yuzuriha A, Otsubo M, Kawaguchi Y, *et al.* Antiviral activities of some new 2,4,6-trisubstituted 1,3,5-triazines having alkoxy and/or alkylamino groups. Heterocycles. 2017; 94(9): 1653. doi: 10.3987/COM-17-13735.
20. Cascioferro S, Parrino B, Spanò V, Carbone A, Montalbano A, Barraja P, *et al.* 1,3,5-triazines: A promising scaffold for anticancer drugs development. Eur J Med Chem. 2017; 142: 523-49. doi: 10.1016/j.ejmech.2017.09.035, PMID 29046238.
21. Roy PS, Saikia BJ. Cancer and cure: A critical analysis. Indian J Cancer. 2016.Gilbertson, R. J. Mapping Cancer Origins. Cell 145, 25-29 (2011); (3): 441-2. doi: 10.4103/0019-509X.200658, PMID 28244479.
22. Gadaleta E, Thorn GJ, Ross-Adams H, Jones LJ, Chelala C. Field cancerization in breast cancer. J Pathol. 2022; 257(4): 561-74. doi: 10.1002/path.5902, PMID 35362092.
23. Okamoto A, Watanabe T, Kamata K, Minaga K, Kudo M. Recent updates on the relationship between cancer and autoimmune pancreatitis. Intern Med. 2019; 58(11): 1533-9. doi: 10.2169/internalmedicine.2210-18, PMID 30713326.
24. Bates JP, Derakhshandeh R, Jones L, Webb TJ. Mechanisms of immune evasion in breast cancer. BMC Cancer. 2018; 18(1): 556. doi: 10.1186/s12885-018-4441-3, PMID 29751789.
25. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017; 50(1): 33. doi: 10.1186/s40659-017-0140-9, PMID 28969709.
26. Merino Bonilla JA, Torres Tabanera M, Mendoza R, L. H. El cáncer de mama en el siglo XXI: de la detección precoz a los nuevos tratamientos. Breast cancer in the 21st century: from early detection to new therapies. Radiologia. 2017; 59(5): 368-79. doi: 10.1016/j.rx.2017.06.003, PMID 28712528.
27. Yeo SK, Guan JL. Breast cancer: multiple subtypes within a tumor? Trends Cancer. 2017; 3(11): 753-60. doi: 10.1016/j.trecan.2017.09.001, PMID 29120751.
28. Johnson RH, Anders CK, Litton JK, Ruddy KJ, Bleyer A. Breast cancer in adolescents and young adults. Pediatr Blood Cancer. 2018; 65(12): e27397. doi: 10.1002/pbc.27397, PMID 30156052.
29. McDonald ES, Clark AS, Tchou J, Zhang P, Freedman GM. Clinical diagnosis and management of breast cancer. J Nucl Med. 2016; 57 Suppl 1: 9S-16S. doi: 10.2967/jnumed.115.157834, PMID 26834110.
30. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010; 4(3): 192-208. doi: 10.1016/j.molonc.2010.04.004, PMID 20452298.
31. Roulot A, Héquet D, Guinebretière JM, Vincent-Salomon A, Lerebours F, Dubot C, *et al.* Tumoral heterogeneity of breast cancer. Ann Biol Clin (Paris). 2016; 74(6): 653-60. doi: 10.1684/abc.2016.1192, PMID 27848916.
32. Alemasova EE, Lavrik OI. Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. Nucleic Acids Res. 2019; 47(8): 3811-27. doi: 10.1093/nar/gkz120, PMID 30799503.
33. Sun X, Tang H, Chen Y, Chen Z, Hu Z, Cui Z, *et al.* Loss of the receptors ER, PR and HER2 promotes USP15-dependent stabilization of PARP1 in triple-negative breast cancer. Nat Cancer. 2023; 4(5): 716-33. doi: 10.1038/s43018-023-00535-w, PMID 37012401.
34. Li G, Lin SS, Yu ZL, Wu XH, Liu JW, Tu GH, *et al.* A PARP1 Protac as a novel strategy against PARP inhibitor resistance via promotion of ferroptosis in p53-positive breast cancer. Biochem Pharmacol. 2022; 206: 115329. doi: 10.1016/j.bcp.2022.115329, PMID 36309080.
35. Padayachee J, Daniels A, Balgobind A, Ariatti M, Singh M. Her-2/Neu and Myc gene silencing in breast cancer: therapeutic potential and advancement in nonviral nanocarrier systems. Nanomedicine (Lond). 2020; 15(14): 1437-52. doi: 10.2217/nnm-2019-0459, PMID 32515263.
36. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Ann Oncol. 2007; 18(6): 977-84. doi: 10.1093/annonc/mdl475, PMID 17229773.
37. Demonty G, Bernard-Marty C, Puglisi F, Mancini I, Piccart M. Progress and new standards of care in the management of HER-2 positive breast cancer. Eur J Cancer. 2007; 43(3): 497-509. doi: 10.1016/j.ejca.2006.10.020, PMID 17223541.
38. Ross JS, Fletcher JA. HER-2/neu (c-erb-B2) gene and protein in breast cancer. Am J Clin Pathol. 1999; 112(1) Suppl 1:S53-67. PMID 10396301.
39. Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. 2019; 20(18): 4331. doi: 10.3390/ijms20184331, PMID 31487867.
40. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20(7): 13384-421. doi: 10.3390/molecules200713384, PMID 26205061.
41. Lohning AE, Levonis SM, Williams-Noonan B, Schweiker SS. A practical guide to molecular docking and homology modelling for medicinal chemists. Curr Top Med Chem. 2017; 17(18): 2023-40. doi: 10.2174/1568026617666170130110827, PMID 28137238.
42. An Overview of Molecular Docking; 2023. Available from: http://www.ijcrt.org.
43. Katritzky AR, Ramsden CA, editors. Handbook of heterocyclic chemistry. 3rd ed. Elsevier; 2010.
44. Grimmett MR. Imidazole and benzimidazole synthesis. Academic Press; 1997.
45. Joule JA, Mills K. Heterocyclic chemistry. 5th ed. Wiley-Blackwell; 2010.

46. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3(11): 935-49. doi: 10.1038/nrd1549, PMID 15520816.
47. Morris GM, Lim-Wilby M. Molecular docking. In: Kukol A, editor. Molecular modeling of proteins. Springer; 2008. p. 365-82. doi: 10.1007/978-1-59745-177-2_19.
48. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comp Chem. 2010; 31(2): 455-61. doi: 10.1002/jcc.21334, PMID 19499576.
49. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235(4785): 177-82. doi: 10.1126/science.3798106, PMID 3798106.
50. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science. 2017; 355(6330): 1152-8. doi: 10.1126/science.aam7344, PMID 28302823.
51. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009; 9(7): 463-75. doi: 10.1038/nrc2656, PMID 19536107.
52. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005; 434(7035): 913-7. doi: 10.1038/nature03443, PMID 15829966.
53. Cascioferro S, Parrino B, Spanò V, Carbone A, Montalbano A, Barraja P, *et al.* 1,3,5-triazines: A promising scaffold for anticancer drugs development. Eur J Med Chem. 2017; 142: 523-49. doi: 10.1016/j.ejmech.2017.09.035, PMID 29046238.
54. Dai Q, Sun Q, Ouyang X, Liu J, Jin L, Liu A, *et al.* Antitumor activity of s-triazine derivatives: A systematic review. Molecules. 2023; 28(11): 4278. doi: 10.3390/molecules28114278, PMID 37298753.
55. Zacharie B, Abbott SD, Duceppe JS, Gagnon L, Grouix B, Geerts L, *et al.* Design and synthesis of new 1,3,5-trisubstituted triazines for the treatment of cancer and inflammation. ChemistryOpen. 2018; 7(9): 737-49. doi: 10.1002/open.201800136, PMID 30258746.
56. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434(7035): 917-21. doi: 10.1038/nature03445, PMID 15829967.
57. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Ann Oncol. 2007; 18(6): 977-84. doi: 10.1093/annonc/mdl475, PMID 17229773.
58. Li G, Lin SS, Yu ZL, Wu XH, Liu JW, Tu GH, *et al.* A PARP1 Protac as a novel strategy against PARP inhibitor resistance via promotion of ferroptosis in p53-positive breast cancer. Biochem Pharmacol. 2022; 206: 115329. doi: 10.1016/j.bcp.2022.115329, PMID 36309080.
59. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20(7): 13384-421. doi: 10.3390/molecules200713384, PMID 26205061.
60. Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. 2019; 20(18): 4331. doi: 10.3390/ijms20184331, PMID 31487867.
61. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010; 4(3): 192-208. doi: 10.1016/j.molonc.2010.04.004, PMID 20452298.
62. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017; 50(1): 33. doi: 10.1186/s40659-017-0140-9, PMID 28969709.
63. Ross JS, Fletcher JA. HER-2/neu (c-erb-B2) gene and protein in breast cancer. Am J Clin Pathol. 1999; 112(1) Suppl 1:S53-67. PMID 10396301.
64. Sun X, Tang H, Chen Y, Chen Z, Hu Z, Cui Z, *et al.* Loss of the receptors ER, PR and HER2 promotes USP15-dependent stabilization of PARP1 in triple-negative breast cancer. Nat Cancer. 2023; 4(5): 716-33. doi: 10.1038/s43018-023-00535-w, PMID 37012401.
65. Kidwai M, Venkataramanan R, Mohan R, Sapra P. Cancer chemotherapy and heterocyclic compounds. Curr Med Chem. 2002; 9(12): 1209-28. doi: 10.2174/0929867023370059, PMID 12052173.
66. Shukla V, Pathak M, Mishra GP, Pandey RK. Pharmacological activities of hybrid derivatives of -s-triazine: a review. Int J Pharmacognosy Pharm Sci. 2019; 1(1): 42-9. doi: 10.33545/27067009.2019.v1.i1a.82.
67. Alemasova EE, Lavrik OI. Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. Nucleic Acids Res. 2019; 47(8): 3811-27. doi: 10.1093/nar/gkz120, PMID 30799503.
68. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016; 16(2): 110-20. doi: 10.1038/nrc.2015.21, PMID 26775620.
69. Demonty G, Bernard-Marty C, Puglisi F, Mancini I, Piccart M. Progress and new standards of care in the management of HER-2 positive breast cancer. Eur J Cancer. 2007; 43(3): 497-509. doi: 10.1016/j.ejca.2006.10.020, PMID 17223541.
70. Padayachee J, Daniels A, Balgobind A, Ariatti M, Singh M. Her-2/Neu and Myc gene silencing in breast cancer: therapeutic potential and advancement in nonviral nanocarrier systems. Nanomedicine (Lond). 2020; 15(14): 1437-52. doi: 10.2217/nnm-2019-0459, PMID 32515263.
71. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol. 2016; 13(11): 674-90. doi: 10.1038/nrclinonc.2016.66, PMID 27184417.
72. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, *et al.* Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011; 121(7): 2750-67. doi: 10.1172/JCI45014, PMID 21633166.
73. Katritzky AR, Ramsden CA, editors. Handbook of heterocyclic chemistry. 3rd ed. Elsevier; 2010.
74. Grimmett MR. Imidazole and benzimidazole synthesis. Academic Press; 1997.
75. Joule JA, Mills K. Heterocyclic chemistry. 5th ed. Wiley-Blackwell; 2010.
76. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3(11): 935-49. doi: 10.1038/nrd1549, PMID 15520816.
77. Morris GM, Lim-Wilby M. Molecular docking. In: Kukol A, editor. Molecular modeling of proteins. Springer; 2008. p. 365-82. doi: 10.1007/978-1-59745-177-2_19.
78. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comp Chem. 2010; 31(2): 455-61. doi: 10.1002/jcc.21334, PMID 19499576.
79. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235(4785): 177-82. doi: 10.1126/science.3798106, PMID 3798106.
80. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science. 2017; 355(6330): 1152-8. doi: 10.1126/science.aam7344, PMID 28302823.
81. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009; 9(7): 463-75. doi: 10.1038/nrc2656, PMID 19536107.
82. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005; 434(7035): 913-7. doi: 10.1038/nature03443, PMID 15829966.
83. Cascioferro S, Parrino B, Spanò V, Carbone A, Montalbano A, Barraja P, *et al.* 1,3,5-triazines: A promising scaffold for anticancer drugs development. Eur J Med Chem. 2017; 142: 523-49. doi: 10.1016/j.ejmech.2017.09.035, PMID 29046238.
84. Dai Q, Sun Q, Ouyang X, Liu J, Jin L, Liu A, *et al.* Antitumor activity of s-triazine derivatives: A systematic review. Molecules. 2023; 28(11): 4278. doi: 10.3390/molecules28114278, PMID 37298753.
85. Zacharie B, Abbott SD, Duceppe JS, Gagnon L, Grouix B, Geerts L, *et al.* Design and synthesis of new 1,3,5-trisubstituted triazines for the treatment of cancer and inflammation. ChemistryOpen. 2018; 7(9): 737-49. doi: 10.1002/open.201800136, PMID 30258746.
86. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434(7035): 917-21. doi: 10.1038/nature03445, PMID 15829967.
87. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Ann Oncol. 2007; 18(6): 977-84. doi: 10.1093/annonc/mdl475, PMID 17229773.
88. Li G, Lin SS, Yu ZL, Wu XH, Liu JW, Tu GH, *et al.* A PARP1 Protac as a novel strategy against PARP inhibitor resistance via promotion of ferroptosis in p53-positive breast cancer. Biochem Pharmacol. 2022; 206: 115329. doi: 10.1016/j.bcp.2022.115329, PMID 36309080.
89. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20(7): 13384-421. doi: 10.3390/molecules200713384, PMID 26205061.
90. Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. 2019; 20(18): 4331. doi: 10.3390/ijms20184331, PMID 31487867.
91. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010; 4(3): 192-208. doi: 10.1016/j.molonc.2010.04.004, PMID 20452298.
92. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017; 50(1): 33. doi: 10.1186/s40659-017-0140-9, PMID 28969709.
93. Ross JS, Fletcher JA. HER-2/neu (c-erb-B2) gene and protein in breast cancer. Am J Clin Pathol. 1999; 112(1) Suppl 1:S53-67. PMID 10396301.
94. Sun X, Tang H, Chen Y, Chen Z, Hu Z, Cui Z, *et al.* Loss of the receptors ER, PR and HER2 promotes USP15-dependent stabilization of PARP1 in triple-negative breast cancer. Nat Cancer. 2023; 4(5): 716-33. doi: 10.1038/s43018-023-00535-w, PMID 37012401.
95. Kidwai M, Venkataramanan R, Mohan R, Sapra P. Cancer chemotherapy and heterocyclic compounds. Curr Med Chem. 2002; 9(12): 1209-28. doi: 10.2174/0929867023370059, PMID 12052173.
96. Shukla V, Pathak M, Mishra GP, Pandey RK. Pharmacological activities of hybrid derivatives of -s-triazine: a review. Int J Pharmacognosy Pharm Sci. 2019; 1(1): 42-9. doi: 10.33545/27067009.2019.v1.i1a.82.
97. Alemasova EE, Lavrik OI. Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. Nucleic Acids Res. 2019; 47(8): 3811-27. doi: 10.1093/nar/gkz120, PMID 30799503.

Cite this article: Senthamarai T, Arivukkarasu NK, Sakthivel E, Seevagavazhuthi A, Natarajan V, Devarasu P, *et al*. argeting Breast Cancer with Triazine Derivatives: A Molecular Docking Analysis of HER2 and PARP1 Inhibition. Pharmacog Res. 2025;17(4):1281-92.