SRI VENKATESWARA INTERNSHIP PROGRAM FOR RESEARCH IN ACADEMICS (SRI-VIPRA)

SRI-VIPRA

Project Report of 2024: SVP- 2401

"A Mini Review on Thiazole Derivatives as Potential Inhibitors of VEGFR-2 and Breast Cancer: A Comparative Study"

IQAC

Sri Venkateswara College

University of Delhi

Benito Juarez Road, Dhaula Kuan, New Delhi

New Delhi -110021

SRIVIPRA PROJECT - 2024

Title of the Project: "A Mini Review on Thiazole Derivatives as Potential Inhibitors of VEGFR-2 and Breast Cancer: A Comparative Study"

Name of Mentor	**:**	**Dr. K. Murali Mohan Achari**	
Name of Department	**:**	**Department of Chemistry**	
Designation	**:**	**Assistant Professor**	

List of students under the SRIVIPRA Project

S. No	Photo	Name of the student	Roll Number	Course	Signature
1		KEERTHANA A V	1222040	B.Sc. Hons Biochemistry	

(Dr. K. Murali Mohan Achari)

Signature of Mentor

CERTIFICATE OF ORIGINALITY

This is to certify that the aforementioned student from Sri Venkateswara College have participated in the summer project **SVP-2401** titled **"A Mini Review on Thiazole Derivatives as Potential Inhibitors of VEGFR-2 and Breast Cancer: A Comparative Study"**. The participant have carried out the research project work under my guidance and supervision from **01st July, 2024** to **30th September 2024**. The work carried out is original and carried out in an online/offline/hybrid mode.

(Dr. K. Murali Mohan Achari)
Signature of Mentor

ACKNOWLEDGEMENT

First and foremost, I would like to express my profound gratitude to my beloved parents for their constant support and encouragement. I owe a deep depth of gratitude to **Dr. K. MURALI MOHAN ACHARI, M.Sc., Ph.D.,** Assistant Professor, Department of Chemistry, Sri Venkateswara College, University of Delhi, for having taken keen interest in guiding me at all stages in the course of my experimental investigations, theoretical studies, discussion and writing during the preparation of this project work. I am grateful for making to have a good feel of the subject and their encouragement throughout my course.

(KEERTHANA A V)

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CHAPTER – I
INTRODUCTION

1. HETEROCYCLIC COMPOUNDS

Heterocyclic compounds represent a vital category of organic molecules defined by the inclusion of heteroatoms, atoms that are not carbon, within their cyclic frameworks (**Fig. 1**). These compounds often feature nitrogen, oxygen, and sulphur, and have attracted considerable attention across various disciplines, especially in biology and medicine.[1] Heterocyclic compounds are broadly classified into two categories: aliphatic and aromatic. These compounds generally feature small ring structures, with some consisting of 3- or 4-membered rings, though the most prevalent ones are made up of 5 to 7-membered rings. A majority of these compounds are 5 or 6-membered rings, typically containing between 1 and 3 heteroatoms in their structures.[2]

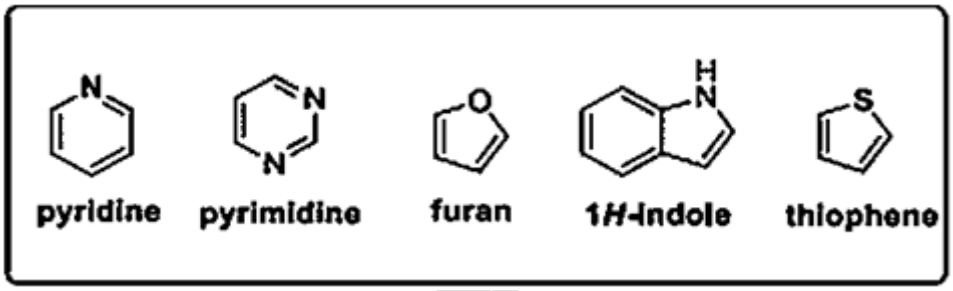


Figure 1. Structures of some heterocyclic compounds

1.1. Importance of Heterocyclic Compounds

1.1.1. Biological Molecules: Heterocyclic rings are key elements in many essential biological molecules.

1.1.2. Medicinal Applications: The pharmaceutical industry extensively utilizes heterocyclic compounds due to their varied biological activities like anticancer, antimicrobial, antiviral etc.

1.1.3. Drug Development: The structural variety of heterocyclic compounds enables medicinal chemists to create molecules with specific biological functions. This diversity is crucial for developing new drugs aimed at a wide range of diseases, including cancer.

1.1.4. Research and Innovation

Ongoing studies in heterocyclic chemistry are continually revealing new compounds with potential uses in treating various illnesses, highlighting the significance of these compounds in drug discovery.[3] Among the extensive range of heterocyclic compounds, thiazole derivatives are particularly notable for their unique five-membered ring structure that includes both nitrogen and sulphur.

The significance of thiazole derivatives in medicinal chemistry has been underscored by numerous studies demonstrating their potential as anticancer agents. Thiazole derivatives have been the focus of extensive research due to their ability to inhibit the growth of cancer cells and promote apoptosis.[4] These compounds can interfere with the cell cycle, halting the division and growth of cancer cells.

2. 1,3-Thiazole Derivatives

Thiazole is a five-membered ring heterocyclic compound and contains sulphur and nitrogen in 1,3 or 1,2 positions (**Fig. 2**).[5] Thiazole is a liquid, yellow in colour and used for preparation of many drugs and dyes [6]. They are found as constituents of animal cells and in the main scaffold of several natural products including vitamins, alkaloids, and pigments.

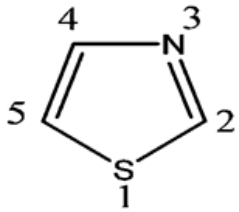


Figure 2. Structure of 1,3-thiazole

Among the various heterocyclic compounds, 1,3-thiazole derivatives have attracted interest due to their wide range of pharmacological activities, especially in the context of cancer therapy. 1,3-Thiazole-based compounds are found in 18 FDA-approved drugs across various therapeutic categories (**Fig. 3**). These include antitumor agents like epothilone and tiazofurin, anti-inflammatory drugs

such as meloxicam, antifungals like isavuconazole, antigout medications like febuxostat, antiulcer treatments like nizatidine, and antibiotics including aztreonam, sulfathiazole, cefepime, and ceftriaxone.[8]

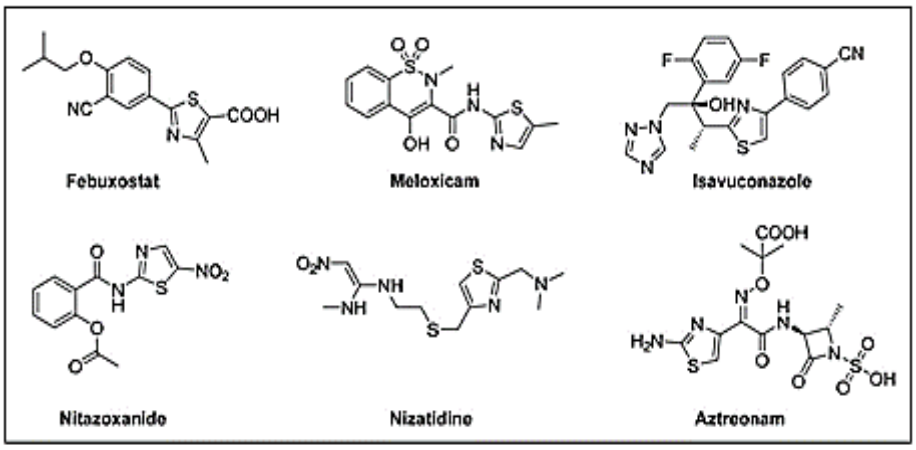


Figure 3. Selected structures of 1,3-thiazoles based FDA drugs

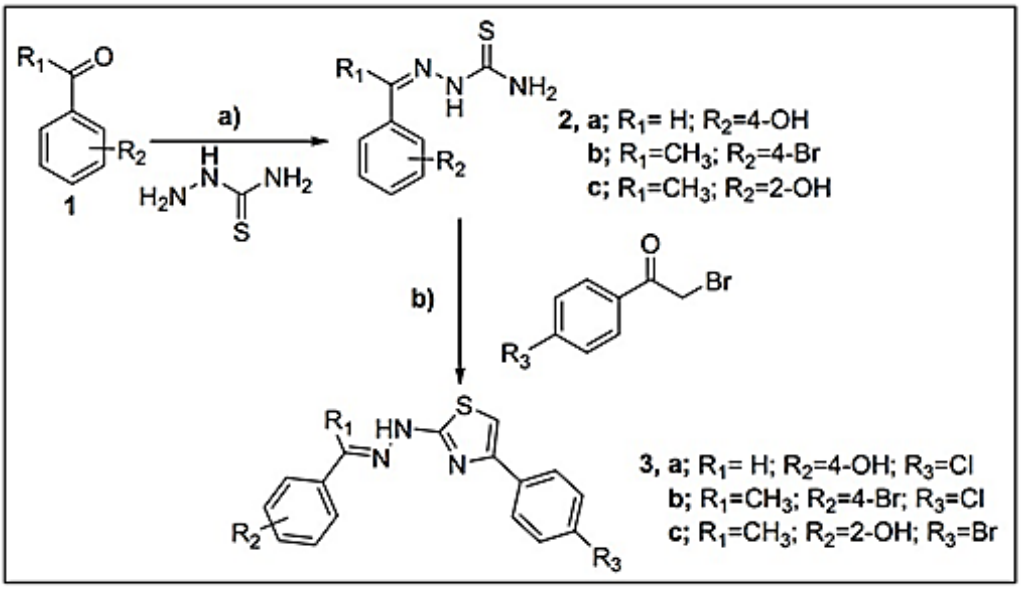
The pharmacological significance of 1,3-thiazole-based compounds has led to increased interest in developing derivatives for potential use in antiviral, antibacterial, antidiabetic, antioxidant, anti-inflammatory, anticancer, and antifungal therapies. Among the 1,3-thiazole analogues, 2-(2-hydrazinyl)-1,3-thiazoles have shown a wide range of therapeutic uses, including antitumor, antiviral and antimicrobial activities.[9] As a result, the chemistry of 2-(2-hydrazinyl)-1,3-thiazoles has garnered significant interest from many researchers.

3. Synthesis and design of Thiazole derivatives

3.1. Core structure synthesis

These compounds were created using a multi-step reaction process, as shown in **Scheme 1**, which depicts the coupling of acetophenone derivatives with phenacyl bromide. This crucial reaction results in the formation of the thiazole core through condensation and cyclization reactions.[10] The straightforward nature of this method allows for the efficient synthesis of various thiazole analogues with different substitution patterns. The flexibility of the reaction

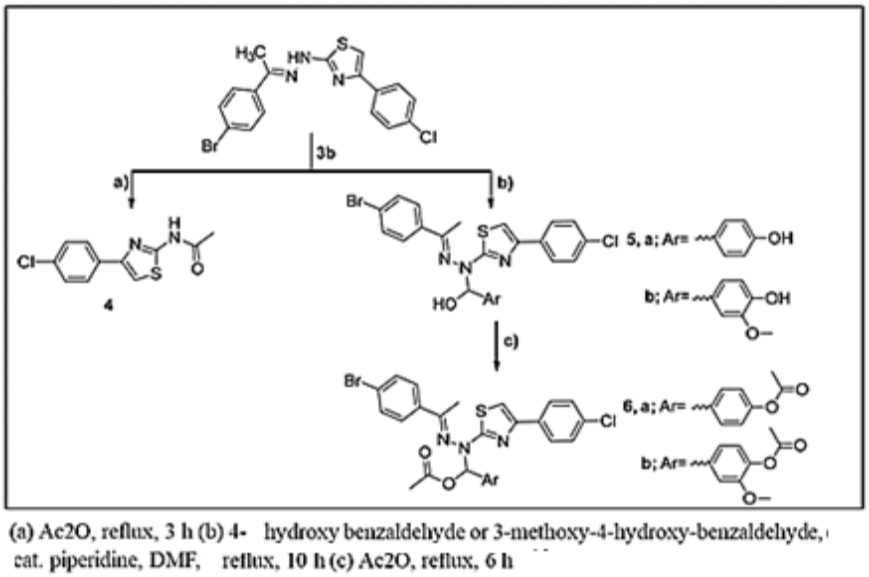
scheme facilitates easy modifications to optimize the biological activity of these molecules, increasing their potential as anticancer agents.



Scheme 1. Synthesis of Novel 1,3-thiazoles

3.2. Structural modification and optimisation

Scheme 2 delves deeper into the chemical adaptability of the thiazole scaffold by outlining further modifications to the core structure. In this phase, extra functional groups are added through acetylation and condensation reactions with substituted aldehydes, leading to new derivatives that exhibit improved pharmacological properties.[11]



(a) Ac2O, reflux, 3 h (b) 4- hydroxy benzaldehyde or 3-methoxy-4-hydroxy-benzaldehyde, cat. piperidine, DMF, reflux, 10 h (c) Ac2O, reflux, 6 h

Scheme 2. Synthesis of 1,3-thiazaoles

This second scheme highlights the possibilities for structural optimization, enabling precise adjustments to both chemical stability and biological effectiveness. Collectively, these schemes illustrate the flexibility of thiazole-based compounds in the realm of drug design.[12]

3.3. Quinazoline-Thiazole Hybrid Molecules

Quinazoline-based thiazole compounds are designed to inhibit the epidermal growth factor receptor (EGFR) kinase, which plays a crucial role in the proliferation of cancer cells.[13] By combining thiazole and quinazoline pharmacophores through molecular hybridization, these hybrid compounds demonstrate dual mechanisms that improve their anticancer effects (**Fig. 4**). The thiazole ring acts as an essential scaffold in this design, offering structural flexibility to the hybrid molecules and facilitating effective kinase inhibition.[14]

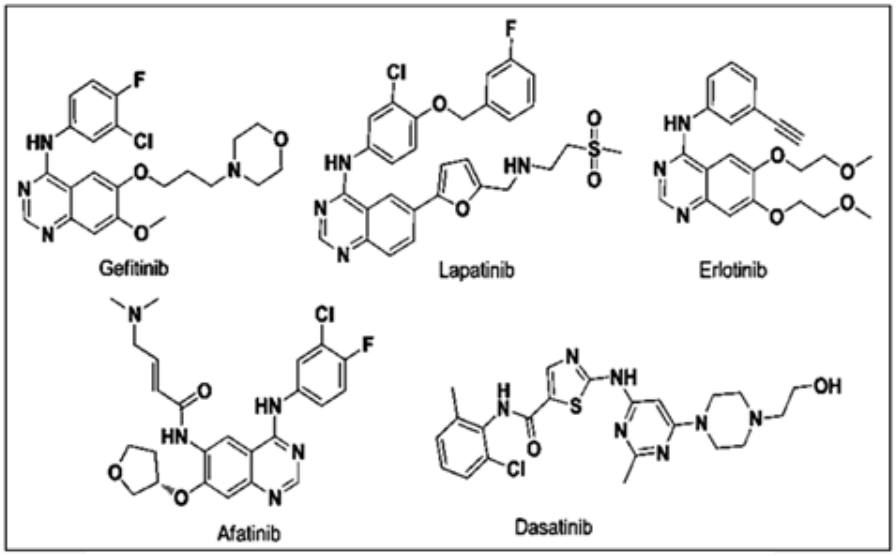


Figure 4. Structures of marked Quinazoline and thiazole based EGFR inhibitors

CHAPTER – II
METHODOLOGY

1. Computer Aided Drug Discovery (CADD)

Computer-Aided Drug Discovery (CADD) has transformed the pharmaceutical industry by tackling the complexities, costs, and time constraints associated with traditional drug development. The drug discovery process, which can take 10 to 15 years and cost between $500 million and $800 million, involves identifying bioactive compounds that effectively interact with specific biological targets like proteins or nucleic acids.[15] Typically, only one out of every 100,000 compounds reach the market, and the journey is fraught with challenges such as toxicity, poor efficacy, or complex synthesis (**Fig. 5 & 6**). CADD is crucial in overcoming these obstacles by utilizing computational tools to streamline and enhance drug design, particularly during the hit-to-lead optimization phase.

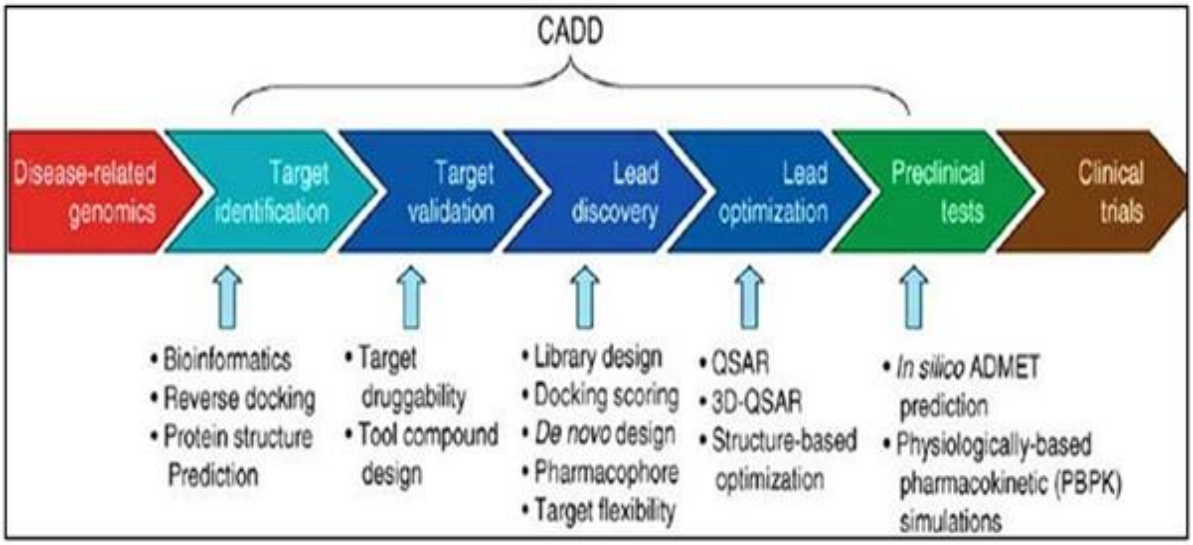


Figure 5. Computer Aided Drug Design

At its essence, CADD relies on structural information about molecular interactions, focusing on aspects like molecular surface geometry, electrostatic forces, hydrophobic interactions, and hydrogen bonding to predict how a compound will bind to a biological target. *In silico* methods, such as molecular docking, virtual screening, and quantitative structure-activity relationship (QSAR) analysis, enable researchers to assess potential drug candidates without

the need for extensive laboratory synthesis. This approach not only cuts costs but also expands the chemical space available for exploration, allowing for the investigation of thousands of compounds in a short period.[16]

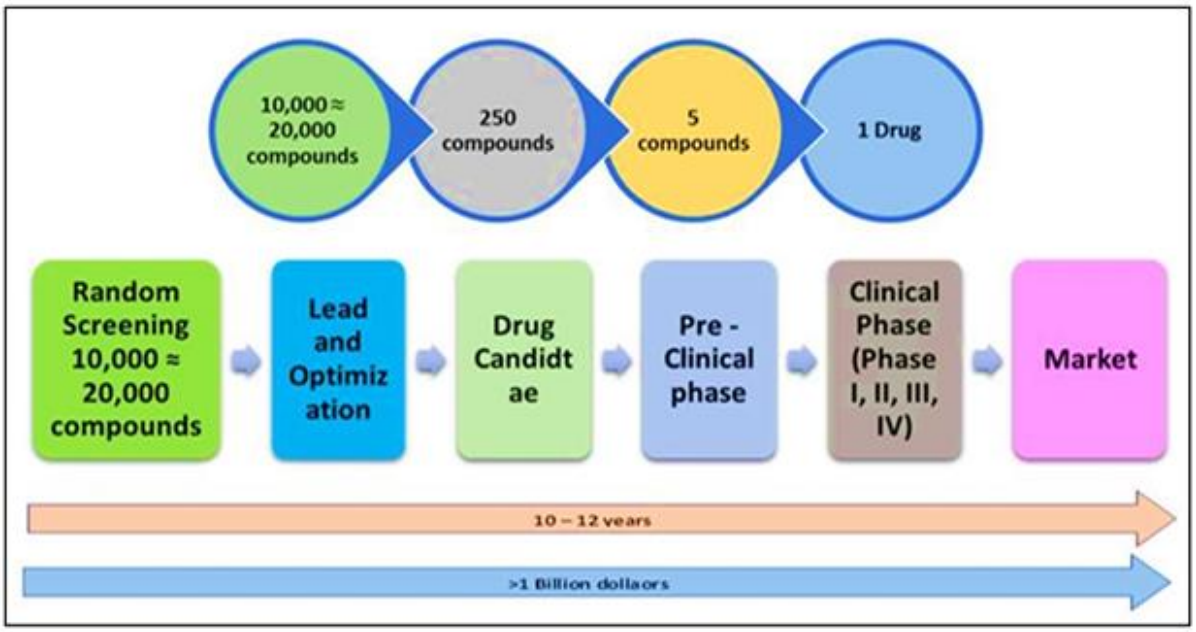


Figure 6. Traditional Drug Research and Development Process

In the research area of thiazoles, CADD serves as a vital tool for identifying and optimizing compounds with potential pharmacological activity. Thiazole derivatives have demonstrated promise across various therapeutic areas due to their heterocyclic structure, which provides flexibility in drug design. By employing CADD techniques, we can model and predict how these thiazole derivatives interact with biological targets, pinpointing key active sites and enhancing their binding affinities.[17] This method accelerates the discovery of lead compounds and reduces the need for expensive synthesis and in vitro testing, making it an invaluable resource in contemporary drug discovery.

1.1 Structure-Based Drug Design (SBDD)

Structure-Based Drug Design (SBDD) is a key strategy in drug development that emphasizes the use of the three-dimensional structures of biological targets, primarily proteins, to create new therapeutic compounds. This method is crucial for discovering innovative drugs, as it allows researchers to closely examine the active or binding sites of these targets.[18] With structural data obtained from techniques like X-ray crystallography or nuclear magnetic resonance (NMR), scientists can design or refine ligands that fit perfectly into the target's active site, improving binding affinity and selectivity. By utilizing computational tools such as molecular docking, SBDD facilitates the swift identification of potential compounds, greatly minimizing the trial-and-error phase typically associated with drug discovery (**Fig. 7**). This targeted approach speeds up the development of new medications, establishing it as a fundamental aspect of contemporary pharmaceutical research.

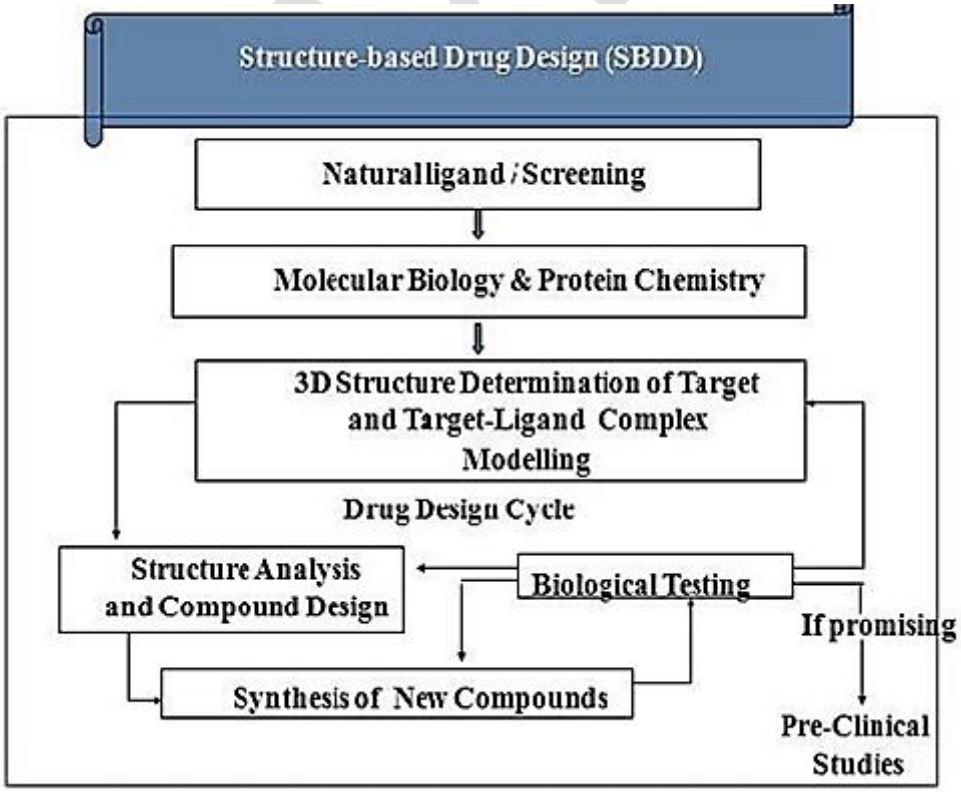


Figure 7. Structure Based Drug Design

1.2. Ligand-Based Drug Design (LBDD)

Ligand-Based Drug Design (LBDD) is an effective approach in drug discovery that emphasizes the study of known ligands—compounds that have demonstrated interactions with a specific biological target. This strategy uses a dataset of reference structures from these ligands to guide the creation of new compounds. By analysing the two-dimensional (2D) or three-dimensional (3D) structures of these ligands, researchers can pinpoint crucial features that influence binding affinity and specificity. In cases where the 3D structure of the target protein is unavailable, LBDD enables the design of new drug candidates based on the properties of known ligands.[19]

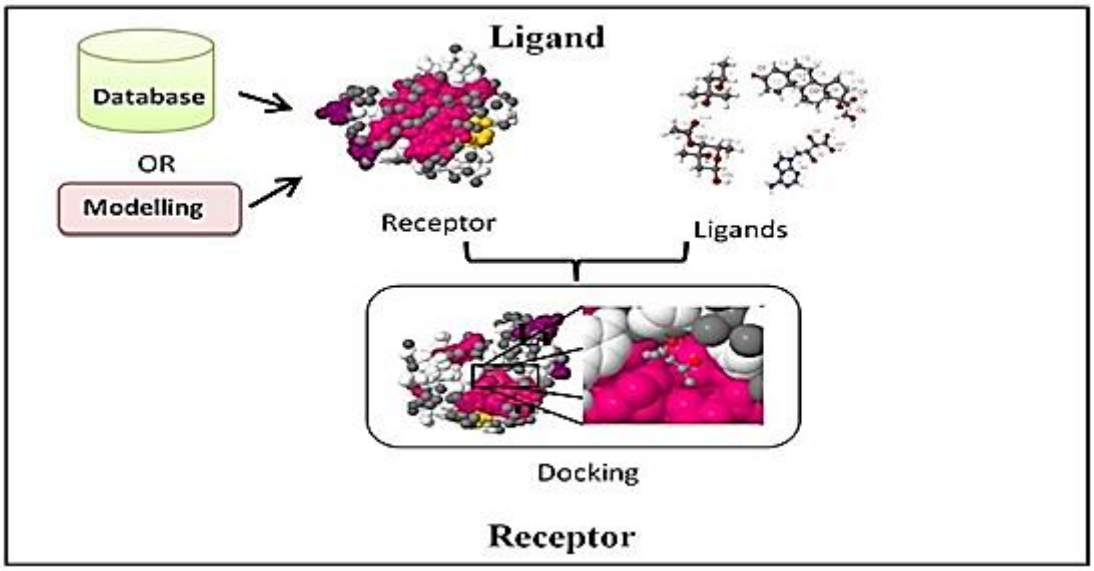


Figure 8. Ligand-Based Drug Design

This method may include techniques like pharmacophore modelling and quantitative structure-activity relationship (QSAR) analysis, which utilize existing knowledge of ligand-target interactions to forecast how new compounds might perform. Ultimately, LBDD acts as a vital complement to structure-based methods, aiding in the identification of potential drug candidates and enhancing the drug discovery process.

CHAPTER – III

MECHANISM OF ACTION

1. VEGFR-2 Inhibition and Angiogenesis Suppression

The first study shows that thiazole derivatives, especially compound 4, demonstrate significant activity against VEGFR-2, a receptor that plays a key role in angiogenesis (the process of forming new blood vessels). By inhibiting VEGFR-2 with an IC50 of 0.093 μM, compound **4** effectively restricts blood supply to tumors, which in turn slows their growth and proliferation (**Table 1**). This mechanism is particularly important in the treatment of breast cancer, where angiogenesis is a major factor in tumor metastasis and survival.[20]

Comp No.	IC_{50} Values (μM)
3c	0.253 ± 0.54
4	0.093 ± 0.22
Sorafenib	0.059 ± 0.35

Table 1. Assessment of VEGFR-2 inhibitory activity of 1,3-thazoles

2. EGFR Kinase Inhibition

The researchers tested quinazoline-thiazole hybrids against various EGFR mutations, finding that the corresponding thiazole compounds **4c** and **4d** exhibited strong inhibitory effects, with IC50 values of 2.86 μM and 3.09 μM, respectively, in MCF-7 cells.[21] Notably, these compounds outperformed the widely used drug erlotinib, especially in cancer cells that show resistance to EGFR inhibitors.

CHAPTER – IV

RESULTS AND DISCUSSION

1. Structural Elucidation of Thiazole Derivatives

The chemical structures of the thiazole derivatives (**Table 2**) were confirmed using advanced spectroscopic techniques. Techniques such as ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry were utilized to verify the successful formation of these compounds.[22] The spectra revealed characteristic peaks associated with thiazole rings and different substituents, confirming the integrity and purity of the synthesized compounds. This structural flexibility highlights the adaptability of thiazole scaffolds in the design of anticancer agents.

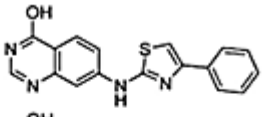
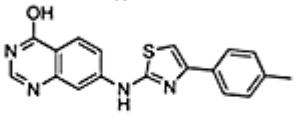
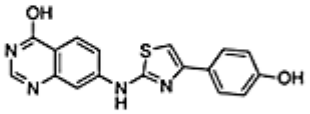
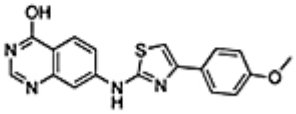
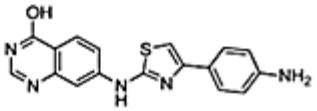
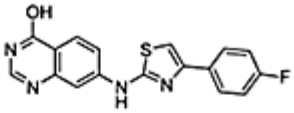
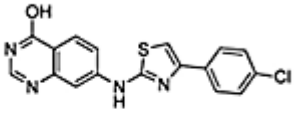
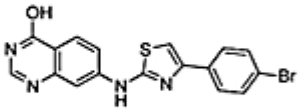
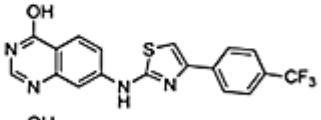
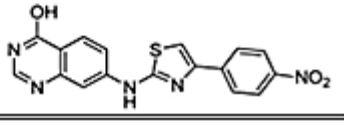
Compound	R	Final structure
4a	-H	
4b	-CH_3	
4c	-OH	
4d	-OCH_3	
4e	-NH_2	
4f	-F	
4g	-Cl	
4h	-Br	
4i	-CF_3	
4j	-NO_2	

Table 2. Structures of Target Compounds (**4a-j**)

2. Activity against Breast Cancer Cells

The synthesized thiazole derivatives were evaluated for their antiproliferative activity against two breast cancer cell lines: MCF-7 and MDA-MB-231. The MTT assay was employed to assess the cytotoxic effects of these compounds. The findings indicated that almost all the thiazole analogues displayed notable antiproliferative activity, with compound **4** emerging as the most effective among those tested.[23]

Compound	IC_{50} (μM)		
	MCF-7	MDA-MB-231	MCF-10A
3a	24.9 ± 1.9	18.65 ± 1.42	NT
3b	31.22 ± 2.38	36.84 ± 2.81	NT
3c	13.66 ± 1.04	17.08 ± 0.13	NT
4	5.73 ± 0.44	12.15 ± 0.93	36.83 ± 05
5a	18.64 ± 1.42	20.72 ± 1.58	NT
5b	32.48 ± 2.47	62.12 ± 0.47	NT
6a	>100	>100	NT
6b	43.81 ± 2.04	77.04 ± 1.95	NT
STU	6.77 ± 0.08	7.03 ± 0.19	26.72 ± 1.26

Table 3. Inhibitory activity of compounds toward the various breast cancer cell lines and epithelial breast cell lines

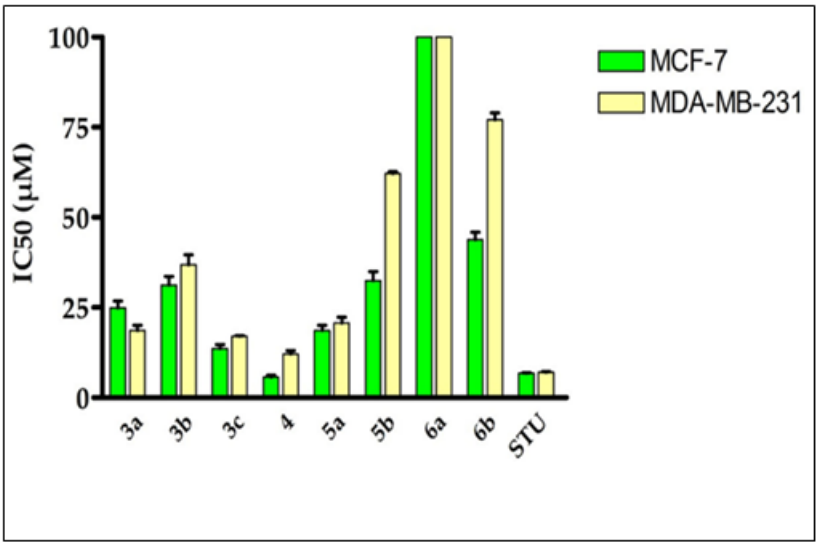


Figure 9. Anti-proliferative activity of thiazole toward MCF-7 and MDA-MB-231 breast cell lines

For MCF-7 cells, compound 4 recorded an IC50 value of 5.73 µM, while for MDA-MB-231 cells, it showed an IC50 of 12.15 µM. These results were comparable to the standard anticancer agent Staurosporine, emphasizing the potential of compound **4** as a strong anticancer candidate (**Table 3 & Fig. 9**). Additionally, none of the compounds tested exhibited significant toxicity towards normal epithelial cells, highlighting their selectivity for cancerous cells.

3. Molecular Docking and VEGFR-2 Inhibition

A comprehensive *in silico* molecular modelling study was carried out to investigate the inhibitory effects of compounds **3c** and **4** on VEGFR2, a crucial receptor involved in angiogenesis. The 3D structure of VEGFR2 (PDB code: 2oh4), which was co-crystallized with a benzimidazole-urea inhibitor, served as a reference for the binding studies. The molecular modelling approach was validated by redocking the original inhibitor prior to evaluating the binding affinities of the test compounds. The docking results indicated that compounds 3c and 4 exhibited strong binding affinities for the VEGFR2 binding pocket, with scores of −8.21 and −10.16 kcal/mol, respectively (**Table 4**).[24] These interactions were thermodynamically favourable and included both hydrophilic and hydrophobic interactions with key amino acid residues in the active pocket.

Protein (PDB Code)	Compound	Hydrophilic Interactions	Distance (A)	Hydrophobic Interactions	S (kcal/mol)
VEGFR2 (*2oh4*)	benzimidazole-urea ligand	Glu883 Glu883 Cys917 Cys917 Asp1044	2.82 2.81 2.6 2.96 2.89	Ala864, Ile886, Leu887, Ile890, Leu1017, Phe919, Phe916, Val914, Leu1033, Ile1042	−11.47
	3c	Glu883 Cys1043 Asp1044	2.99 3.58 3.44	Val846, Ile886, Leu887, Val897, Val912, Val914, Leu1033, Phe1045	−8.21
	4	Glu883 Glu883 Ile1023 Cys1043 Asp1044	1.82 3.32 3.42 3.22 2.97	Val897, Leu887, Ile886, Ile1045	−10.16

Table 4. Docking score and interactions of compounds **3c** and **4** with VEGFR2 (PDB: 2oh4) protein

Compound **3c** established critical interactions with residues Asp1044, Glu883, and Cys1043, which were further stabilized by additional hydrophobic interactions. In contrast, compound **4** interacted with essential residues Glu883, Cys917, and Asp104, while also engaging with Ile1023 and Cys1043.[25] Both compounds benefited from hydrophobic interactions with nonpolar amino acid residues, enhancing the stability of their binding. Overall, the study demonstrated that the inhibitory activity of these compounds is closely linked to their capacity to bind to the active pocket of VEGFR2, suggesting their potential as effective VEGFR2 inhibitors.

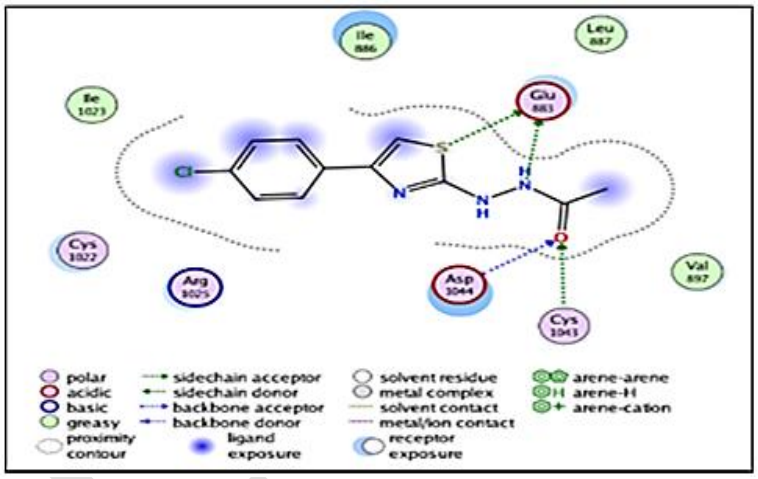


Figure 10. The 2D molecular Docking interactions of the benzimidazole-urea ligand compound **4** into the binding pocket of VEGFR2 (PDB: 2oh4) protein

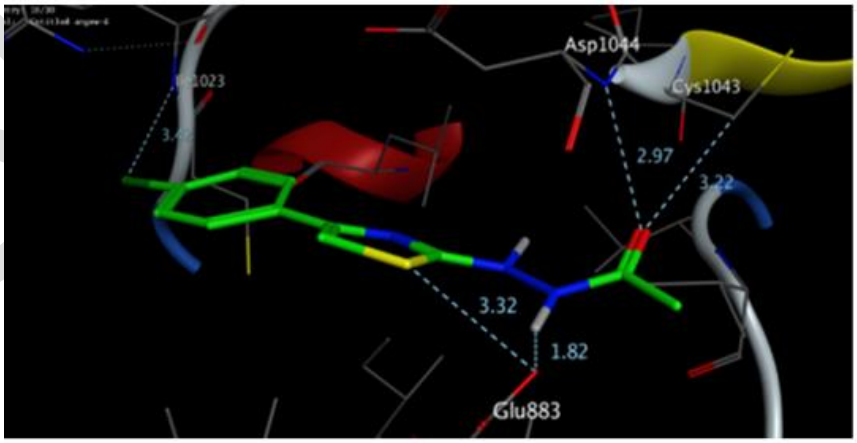


Figure 11. The 3D molecular Docking interactions of the benzimidazole-urea ligand compound **4** into the binding pocket of VEGFR2 (PDB: 2oh4) protein

4. Quinazoline-Based Thiazole Compounds and EGFR Kinase Inhibition

Quinazoline-based thiazole compounds were developed as inhibitors of the EGFR kinase. These compounds were evaluated against MCF-7, HepG2, and A549 cancer cell lines. Notably, compounds 4i and 4j demonstrated remarkable activity, with IC50 values of 2.86 µM and 3.09 µM in MCF-7 cells, respectively. These results surpassed those of erlotinib, a well-known EGFR inhibitor.

Compound	IC_{50} (µM)			
	MCF-7	HepG2	A549	Vero
4a	6.21 ± 0.33	11.86 ± 0.71	24.73 ± 0.95	>50
4b	6.28 ± 0.58	12.59 ± 1.02	27.04 ± 1.09	>50
4c	7.43 ± 0.91	14.16 ± 0.83	31.16 ± 0.97	>50
4d	9.75 ± 1.03	17.28 ± 0.98	24.97 ± 1.14	>50
4e	8.29 ± 0.44	15.03 ± 0.81	29.61 ± 1.22	>50
4f	3.71 ± 0.47	7.92 ± 0.63	19.02 ± 0.83	>50
4g	4.14 ± 0.69	9.36 ± 1.15	20.84 ± 1.24	>50
4h	4.92 ± 0.31	9.85 ± 0.97	22.86 ± 1.06	>50
4i	2.86 ± 0.31	5.91 ± 0.45	14.79 ± 1.03	>50
4j	3.09 ± 0.45	6.87 ± 0.59	17.92 ± 0.95	>50
Erlotinib	3.16 ± 0.22	6.83 ± 0.51	19.42 ± 1.28	>30

Table 5. Cytotoxicity of compounds on Cancer Cell lines

The quinazoline-thiazole hybrids were effective in inhibiting various EGFR mutations, such as L858R/T790M and L858R/T790M/C797S, which are associated with resistance to conventional therapies.[26] Molecular docking studies indicated that these compounds fit effectively into the EGFR active site, establishing stable interactions that inhibit the kinase activity responsible for the proliferation of cancer cells**.**

5. Molecular Docking and EGFR Inhibition

Molecular docking studies demonstrated a robust interaction between quinazoline-based thiazole compounds and the EGFR kinase domain, especially in relation to mutations linked to drug resistance. The docking models revealed that compounds **4i** and **4j** established stable hydrogen bonds and hydrophobic interactions with the mutant EGFR kinase domains, effectively inhibiting the enzymatic activity required for cancer cell proliferation. [26]

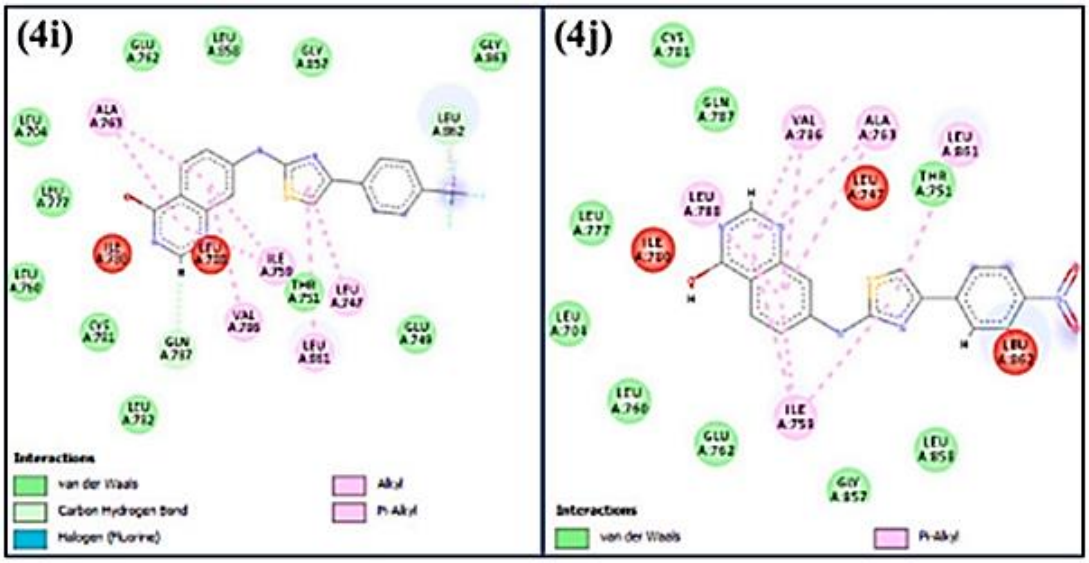


Figure 12. The 2D molecular Docking interactions of the potent compounds **4g, 4i** and **4j** into the binding pocket of target protein (PDB: 6LUD) protein

6. Efficacy and Future Potential

These studies emphasize the potential of thiazole-based compounds in anticancer drug development. The results from these studies not only highlight the effectiveness of thiazole derivatives in breast cancer but also demonstrate the versatility of thiazole as a scaffold for developing multi-target drugs. The ability of quinazoline-thiazole hybrids to inhibit EGFR mutations makes them promising candidates for further development, particularly in cancers with drug resistance. While these compounds have demonstrated potent activity *in vitro*, further research should focus on *in vivo* studies to evaluate their therapeutic potential.

Additionally, optimizing the pharmacokinetic properties and reducing possible side effects are crucial steps toward clinical development.

CHAPTER – V
CONCLUSION

V. CONCLUSION

Thiazole-based compounds have shown great promise as versatile frameworks in the creation of new anticancer agents. The studies reviewed here emphasize the encouraging biological activity of these derivatives, especially in targeting crucial cancer pathways like VEGFR-2 and EGFR kinases. The ability of 1,3-thiazole derivatives to inhibit the proliferation of breast cancer cells and induce cell cycle arrest and apoptosis makes them strong candidates for breast cancer treatment. Additionally, the quinazoline-thiazole hybrids have demonstrated powerful inhibitory effects against EGFR mutations, providing a potential solution to the issue of drug resistance in cancers such as non-small cell lung cancer (NSCLC).

The ease of chemical modification, along with their robust molecular interactions with key cancer-related proteins, highlights the potential of thiazole-based compounds in developing multi-target anticancer therapies. However, while the *in vitro* findings are promising, further research, including *in vivo* studies and clinical trials, is essential to assess their therapeutic efficacy, pharmacokinetics, and safety profile. Optimizing these compounds for human application could lead to more selective and effective treatments for cancer patients, addressing some of the current limitations of existing therapies. In summary, thiazole-based compounds, with their distinctive structural characteristics and strong anticancer activities, represent an exciting new direction in targeted cancer therapy.

CHAPTER – VI
REFERENCES

VI. REFERENCES

1. Al-Mulla, Abbas. "A review: biological importance of heterocyclic compounds." *Der Pharma Chemica* 9.13 (**2017**): 141-147.
2. Saini, M. S., Kumar, A., Dwivedi, J., & Singh, R. (**2013**). A review: biological significances of heterocyclic compounds. *Int. J. Pharm. Sci. Res*, 4(3), 66-77.
3. Qadir, T., Amin, A., Sharma, P. K., Jeelani, I., & Abe, H. (**2022**). A review on medicinally important heterocyclic compounds. *The Open Medicinal Chemistry Journal*, 16(1).
4. Mahajan, N. D., & Jain, N. (**2021**). Heterocyclic compounds and their applications in the field of biology: A detailed study. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO, 13223-13229.
5. Fuster M. D., Mitchell A. E., Ochi H. and Shibamoto T.: Antioxidative activities of heterocyclic compounds formed in brewed coffee, *J. Agr. Food Chem*. **2000**, 11(48) 5600- 5603.
6. Anwar, Rebaz & Koparir, Pelin & Koparir, Metin. (2021). SYNTHESIS OF 1,3-THIAZOLE DERIVATIVES. INDIAN DRUGS. 58. 10.53879/id.58.01.12427.
7. Kempson J., 5.4 Hantzsch Thiazole Synthesis. Name Reactions in Heterocyclic Chemistry II. **2011**, 299.
8. Waks, A.G.; Winer, E.P. Breast Cancer Treatment: A Review. JAMA **2019**, 321, 288–300. [CrossRef]
9. Loibl, S.; Poortmans, P.; Morrow, M.; Denkert, C.; Curigliano, G. Breast Cancer. Lancet **2021**, 397, 1750–1769. [CrossRef]
10. Arora, S.; Narayan, P.; Osgood, C.L.; Wedam, S.; Prowell, T.M.; Gao, J.J.; Shah, M.; Krol, D.; Wahby, S.; Royce, M.; et al. U.S. FDA Drug Approvals for Breast Cancer: A Decade in Review. Clin. Cancer Res. Off. *J. Am. Assoc. Cancer Res*. **2022**, 28, 1072–1086. [CrossRef] [PubMed]
11. An, J.; Peng, C.; Xie, X.; Peng, F. New Advances in Targeted Therapy of HER2-Negative Breast Cancer. *Front. Oncol*. **2022**, 12, 828438. [CrossRef]
12. Cui, W.; Aouidate, A.; Wang, S.; Yu, Q.; Li, Y.; Yuan, S. Discovering Anti-Cancer Drugs via Computational Methods. *Front. Pharmacol*. **2020**, 11, 733. [CrossRef]
13. Sabir, S.; Alhazza, M.I.; Ibrahim, A.A. A Review on Heterocyclic Moieties and Their Applications. *Catal. Sustain. Energy* **2016**, 2, 99–115. [CrossRef]
14. Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K.K.; Jonnalagadda, S.B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, 25, 1909. [CrossRef]
15. Novel 1,3-Thiazole Analogues with Potent Activity against Breast Cancer: A Design, Synthesis, In Vitro, and In Silico Study Manar G. Salem 1 , Dina M. Abu El-Maaty 2 , Yassmina I. Mohey El-Deen 1 , Basem H. Elesawy 3 , Ahmad El Askary 4 , Asmaa Saleh 5 , Essa M. Saied 6,7,* and Mohammed El Behery.
16. Taylor, A.P.; Robinson, R.P.; Fobian, Y.M.; Blakemore, D.C.; Jones, L.H.; Fadeyi, O. Modern Advances in Heterocyclic Chemistry in Drug Discovery. *Org. Biomol. Chem*. **2016**, 14, 6611–6637. [CrossRef]

17. Petrou, A.; Fesatidou, M.; Geronikaki, A. Thiazole Ring-A Biologically Active Scaffold. *Mol. Basel Switz.* **2021**, 26, 3166. [CrossRef]
18. Scott, K.A.; Njardarson, J.T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, 376, 5. [CrossRef] [PubMed]
19. Makam, P.; Thakur, P.K.; Kannan, T. In Vitro and in Silico Antimalarial Activity of 2-(2-Hydrazinyl) Thiazole Derivatives. Eur. J. Pharm. Sci. 2014, 52, 138–145. [CrossRef]
20. Design, synthesis, anticancer activity and docking studies of novel quinazoline-based thiazole derivatives as EGFR kinase inhibitors. Raghu, M.S. et al. Heliyon, Volume 9, Issue 9, e20300
21. M. Al-Anazi, M. Khairuddean, B.O. Al-Najjar, M.M. Alidmat, N.N.S.N. Mohamed Kamal, M. Muhamad, Synthesis, anticancer activity and docking studies of pyrazoline and pyrimidine derivatives as potential epidermal growth factor receptor (EGFR) inhibitors, *Arab. J. Chem.* 15 (**2022**), 103864.
22. S.V. Sharma, D.W. Bell, J. Settleman, D.A. Haber, Epidermal growth factor receptor mutations in lung cancer, *Nat. Rev. Cancer* 7 (**2007**) 169–181.
23. [38] C.A. Eberlein, D. Stetson, A.A. Markovets, K.J. Al-Kadhimi, Z. Lai, P.R. Fisher, C.B. Meador, P. Spitzler, E. Ichihara, S.J. Ross, M.J. Ahdesmaki, A. Ahmed, L. E. Ratcliffe, E.L. O'Brien, C.H. Barnes, H. Brown, P.D. Smith, J.R. Dry, G. Beran, K.S. Thress, B. Dougherty, W. Pao, D.A. Cross, Acquired resistance to the mutant-selective EGFR inhibitor AZD9291 is associated with increased dependence on RAS signalling in preclinical models, Cancer Res. 75 (2015) 2489–2500.
24. C.H. Yun, K.E. Mengwasser, A.V. Toms, M.S. Woo, H. Greulich, K.K. Wong, M. Meyerson, M.J. Eck, The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP, *Proc. Natl. Acad. Sci.* U.S.A. 105 (**2008**) 2070–2075.
25. A. Becker, A.V. Wijk, E.F. Smit, P.E. Postmus, Side-effects of long-term administration of erlotinib in patients with non-small cell lung cancer, *J. Thorac. Oncol.* 5 (**2010**) 1477–1480.
26. S.S. Kaufmann, M. Pless, Acute fatal liver toxicity under erlotinib, *Case Rep. Oncol.* 3 (**2010**) 182–188.