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Review Paper

Synthesis, Characterization, Molecular Docking Studies Benzothiazole Anti-breast Cancer Agents

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ABSTRACT

Cancer is the main cause of mortality worldwide, accounting for the majority of deaths. There is a therapeutic need for innovative, selective anti-tumor medicines that avoid most of the undesirable negative reactions linked to current chemotherapy regimens. The receptor for epidermal growth factor (EGFR) is a membrane glycoprotein, and mutations that cause EGFR overexpression or overactivity have been linked to a range of human malignancies. Substituted 1, 3-benzothiazole derivatives are an important class of heterocyclic compounds. It is a combination of two rings six membered and five membered and both the rings are responsible for the therapeutic activity. Benzothiazole is a class of heterocyclic compound having two hetero atoms namely Sulphur and nitrogen. The analogues of benzothiazole and its derivatives have a significant role in research area especially in synthetic, medicinal and pharmaceutical chemistry because of its biological and pharmacological properties. Our study's major goal is to disseminate up-to-date knowledge regarding synthesised Benzothiazole analogues and related biological activity against a variety of disorders. The benzothiazole possesses a wide spectrum of biological activities such as antimicrobial, anticancer, antioxidant, anti-Inflammatory, anticonvulsant, antimalarial and some miscellaneous Activity. Hence, various methodologies have been Accomplished to synthesize benzothiazole compounds considering the purity, yield, and selectivity of the products.

INTRODUCTION

The field of medicinal chemistry is the one area of exploration that directly affects the health, weal, and development of people. Medicinal chemistry works at the boundary of synthetic organic chemistry and biology with top focus on medicine development. In particular, the study of heterocyclic chemistry is one of the most typical, but inversely important branches of organic chemistry, constituting one of the wide areas of exploration for further than a century. In recent

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times, there has been a growing interest pertaining to the conflation and natural progression of bioactive composites in the field of organic chemistry Benzothiazole is a heterocyclic compound having a thiazole ring. Thiazole having five membered ring fused with benzene gives the benzothiazole. The thiazoles and benzothiazoles are set up in a wide variety of bioactive moity's and natural products. The terrestrial and marine organism's microorganisms have been a prominent source of these heterocyclic.[1] These naturally being secondary metabolites or polypeptides are frequently bioactive and a large bulk of Literature is being published related to their insulation, chemistry and biology. It's a taintless and slightly thick in nature with a boiling point of 227- 228 °C, the viscosity and molar mass of benzothiazole is1.644 gm/ ml and139.19 g/ spook independently. The numbering is starting from sulphur snippet. A variety of synthetic pathways have been accomplished for the formation of benzothiazole derivatives Benzothiazole and its derivations have been of great scientific Exploitation and interest as these are accompanied with nearly all the natural and pharmacological conditioning, like antibacterial, antiviral, antidepressant, analgesic, anticonvulsant, Antiprotozoal, antimalarial, anticancer, treat disinclinations, gene Modulating conditioning, anti-schizophrenia, anti-hypertension, Anti-inflammation, anti-HIV infections and numerous further[2]

1.Breast cancer

Breast cancer remains a formidable adversary in the landscape of global health challenges, with its intricate pathogenesis and diverse clinical manifestations posing significant obstacles to effective treatment and prevention. As the global incidence of this disease continues to rise,it is imperative to unravel the multifaceted nature of breast cancer to develop effective therapeutic strategies. Despite advancements in early detection and therapeutic strategies, the disease exhibits a complex etiology that necessitates a deeper understanding of its molecular underpinnings and risk factors. [3]There are many factors affecting the tumorigenesis of breast and cancer, and evidence illustrates the intricate interplay of genetic, environmental, and lifestyle factors that contribute to that process. Understanding these factors can help in breast cancer prevention and early detection. In addition, the progression of tumor is influenced by various factors operating through distinct mechanisms (such as tumor stemness, intra-tumoral microbiota, and circadian rhythms), and a comprehensive investigation into these mechanisms
is essential for identifying potential clinical therapeutic targets.[4]

1.2 Epidemiology and risk factors

Breast cancer is the most frequently diagnosed cancer globally and a leading cause of women's death. In 2024 alone, it surpassed lung cancer as the most diagnosed cancer type worldwide, with over 2.3 million new cases every year (In India, it is the leading cancer diagnosed in the females, representing approximately 27% of all the cancers This increase in number is because of aging populations, lifestyle changes, and enhanced monitoring and screening in both low- and high-income nations. Developed countries including United States of America, the United Kingdom, and Canada reported the maximum cases. However, the highest mortality was reported by the low- and middle-income countries including India, Brazil, because of a lack of proper treatment and advanced healthcare facilities for early diagnosis and screening Socioeconomic, racial, and ethnic distribution within countries further contributes to the variation in breast cancer pathogenesis. For instance, Yedjou et al. reported lower death rates in the United States in white

women compared to African American and Hispanic women with higher mortality rates. In addition, African Americans have higher BRCA1 frequency are more prone to develop TNBC with poor clinical outcomes compared to women of European origin [5]

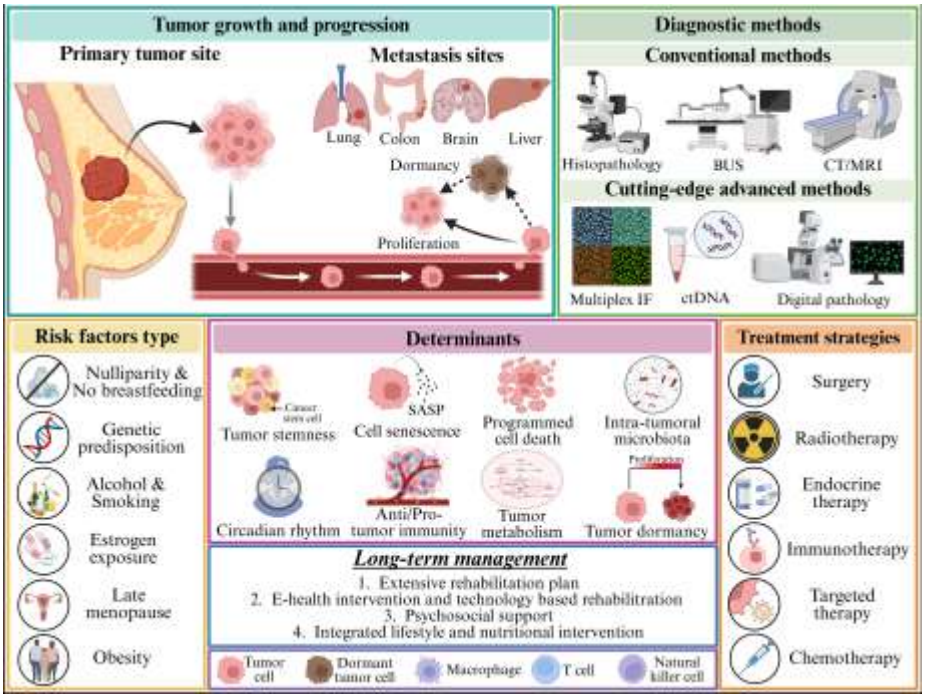

FIGURE 1

Breast cancer pathogenesis and treatment overview. Breast cancer is one of the most diagnosed cancers in women worldwide. In this figure we have shown its origin (primary breast tissue) and various sites where it can metastasize, such as the liver, brain, colon, lung, etc. Breast cancer occurs due to several factors, including genetic predisposition, nulliparity and no breastfeeding, hormonal factors (for example, estrogen exposure), lifestyle factors such as obesity, smoking, and alcohol consumption, and more. The tumor growth and progression are driven by several factors, such as tumor stemness, cell senescence, programmed cell death, microbiota present within and around tumors, circadian rhythm, immunological role, tumor metabolism, and tumor dormancy. Breast cancer diagnosis can be done using both conventional and advanced technologies such as histopathology, liquid biopsies (circulating tumor DNA, tumor-derived exosomes, etc.), imaging techniques (CT, MRI), immunofluorescence assay, digital pathology, etc. Breast cancer can be treated using several strategies, such as surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, and endocrine therapy. Long-term management is very important, as it impacts patients' overall health and survival outcome. BUS, B-scan ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; IF, immunofluorescence; ctDNA, circulating tumor DNA.BioRender.com was used to create the diagram.[6]

1.3 Molecular classification of breast cancer

Pathologically, breast cancer is classified into two major categories: (i) breast invasive carcinoma, which accounts for 70- 75% of the cases, and (ii)

lobular carcinoma, accounting for 12-15%of the cases. Moreover, for accurate prognostic evaluation and clinical decision-making, breast cancer is grouped into four groups. This classification is based on immunohistochemistry (IHC) staining results and expression of hormone receptors ER,

3.1 Luminal A subtype
3.2 Luminal B subtype
3.3 HER2 subtype
3.4 Triple negative breast cancer [7]

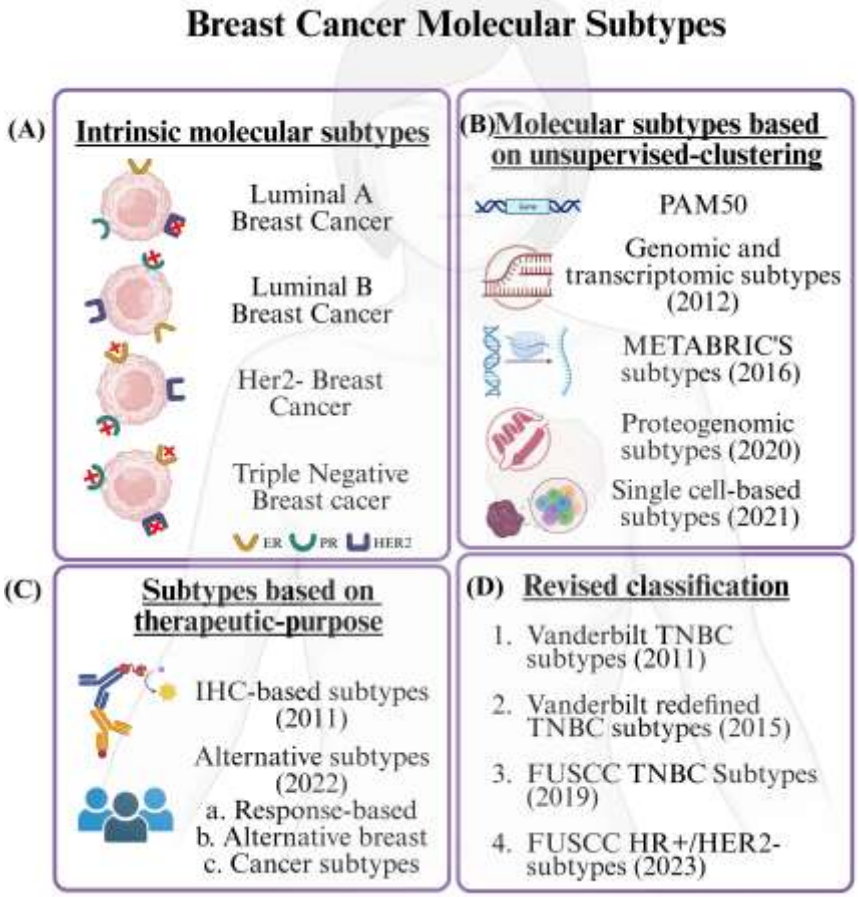

FIGURE 2

Breast cancer classification. Breast cancer has been classified based on several factors. In this diagram, we have shown different classifications proposed over the years based on several factors. (A) In the first section, we present the intrinsic molecular subtypes, which are mainly defined bygene expression profiling (e.g., PAM50), but they are commonly written and reported in clinical practice using immunohistochemical (IHC) markers, i.e., Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor (HER2). Based on the presence or absence of these markers, this subtype is classified as luminal (A/B), HER2, or basal or triple-negative breast cancer (TNBC). In section (B) we reportedsubtypes of breast cancer that have been proposed based on unsupervised machine learning techniques. These include intrinsic subtypes, the widely accepted PAM50 classification, subtypes derived from genomic and transcriptomic data, METABRIC's subtype, proteogenomic subtypes (which are based

on protein and post-translational modifications), and advanced subtypes such as those identified through single-cell analysis. (C) Breastcancer subtypes have also been proposed as per patients' responses to various treatments. Two such common subtypes include the IHC-based subtype and alternative subtypes. (D) Lastly, we have subtypes that have been reclassified based on parameters such as gene expression, proliferation signatures, etc. Common ones include the classification proposed by Vanderbilt for classifying TNBC subtypes, FUSCC TNBC subtypes, and FUSCC HR+/HER2- subtypes. IHC, Immunohistochemistry; TNBC, Triple Negative Breast Cancer; FUSCC, Fudan University Shanghai Cancer Center; HR, Hormone Receptors; HER2, Human Epidermal Growth Factor Receptor 2. BioRender.com was used to create the diagram.[8]

1.4. Mechanisms driving breast cancer

For any type of cancer, including breast, the progression of the tumor is characterized by local recurrence, metastasis, and the development of therapy resistance, all of which pose a challenge that needs urgent attention. Advancements in experimental protocols and sequencing technologies over the time have led to significant achievements in understanding the underlying mechanisms driving breast cancer. Below, we highlight some of the key factors contributing to the progression of breast cancer (Figure 3) [9]

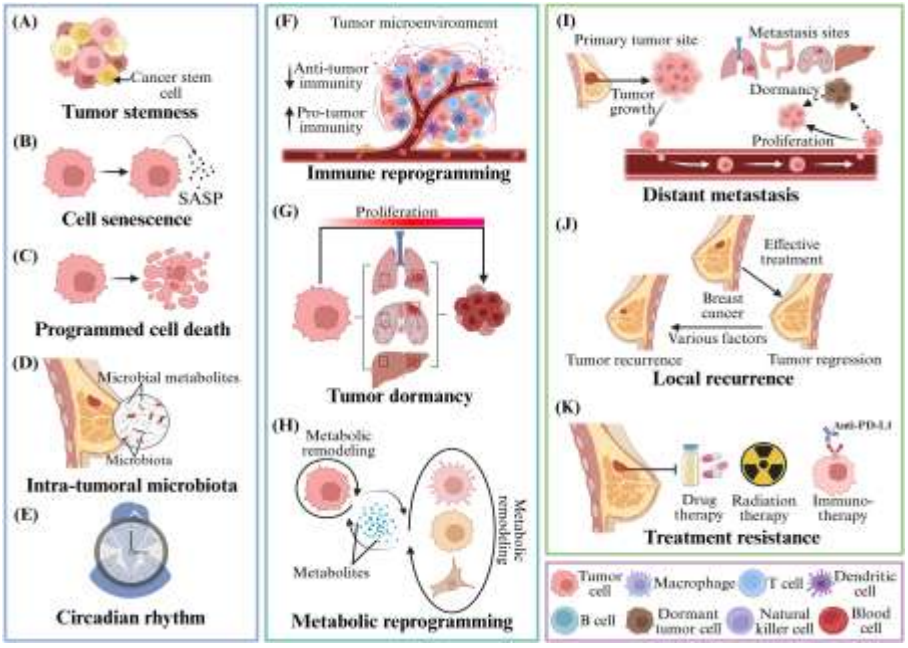

FIGURE 3

Breast cancer progression regulating factors. Numerous factors contribute to breast cancer progression, including (A) tumor stemness, such as the role of cancer stem cells; (B) cell senescence, such as the role of SASP; (C) programmed cell death; (D) microbiota and microbial metabolites; (E) circadian rhythm; and (F) the role of immune programming. (G) Tumor dormancy; (H) Metabolic reprogramming. These factors are responsible for (I) local tumor recurrence, (J) metastasis to distant organs, and (K) resistance to treatment. SASP, Senescence Associated Secretory Phenotype. BioRender.com was used to create the diagram[10]

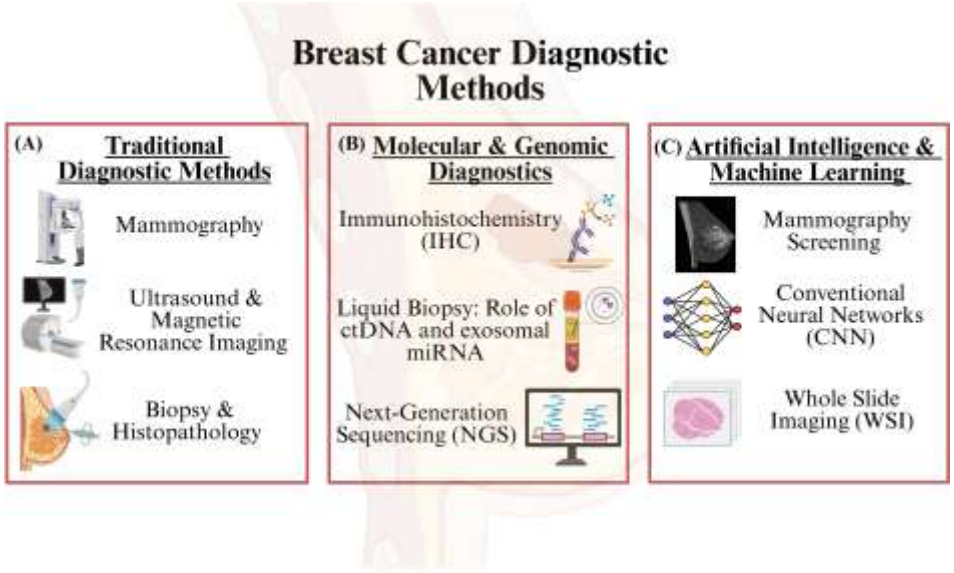

FIGURE 4

Breast cancer diagnostic methods. Breast cancer can be diagnosed via several methods. (A) In the first section, we present traditional diagnostic methods that have been implemented over the years, such as mammography, ultrasound, magnetic resonance imaging, and histopathology. (B) In the second section, we mention various molecular and genomic methods associated with diagnosis, including immunohistochemistry technique, liquid biopsy (circulating DNA, exosomal miRNA, lncRNA, etc.), and next-generation sequencing techniques. (C) Lastly, I have mentioned advanced artificial intelligence and machine learning-based diagnosis techniques, which include deep learning models developed using whole slide imaging for the diagnosis, AI-based models developed using mammography screening, and more. BioRender.com was used to create the diagram.[11]

1.5 Treatment strategies for breast cancer

The strategies for treating breast cancer have progressed in tandem with our understanding of the disease's molecular and pathological heterogeneity, surpassing the notion of a universalapproach. Current treatment includes radiation, chemotherapy, surgery, hormonal therapy, targeted therapies, and emerging immunotherapies. Appropriate treatment is decided based on

tumor stage, grade, status of receptor, genetic mutations, patient'sage, overall health, and more. With the advancements in the personalized medicine approach, clinicians design treatment to maximize benefits and efficacy with minimum side effects and toxicity. Here, we have discussed these treatment strategies, exploring them from traditional to modern approaches[12]

5.1 Surgical interventions

5.2 Radiation therapy

5.3 Systemic therapies

5.4 Machine learning guided therapeutic decision making [13]

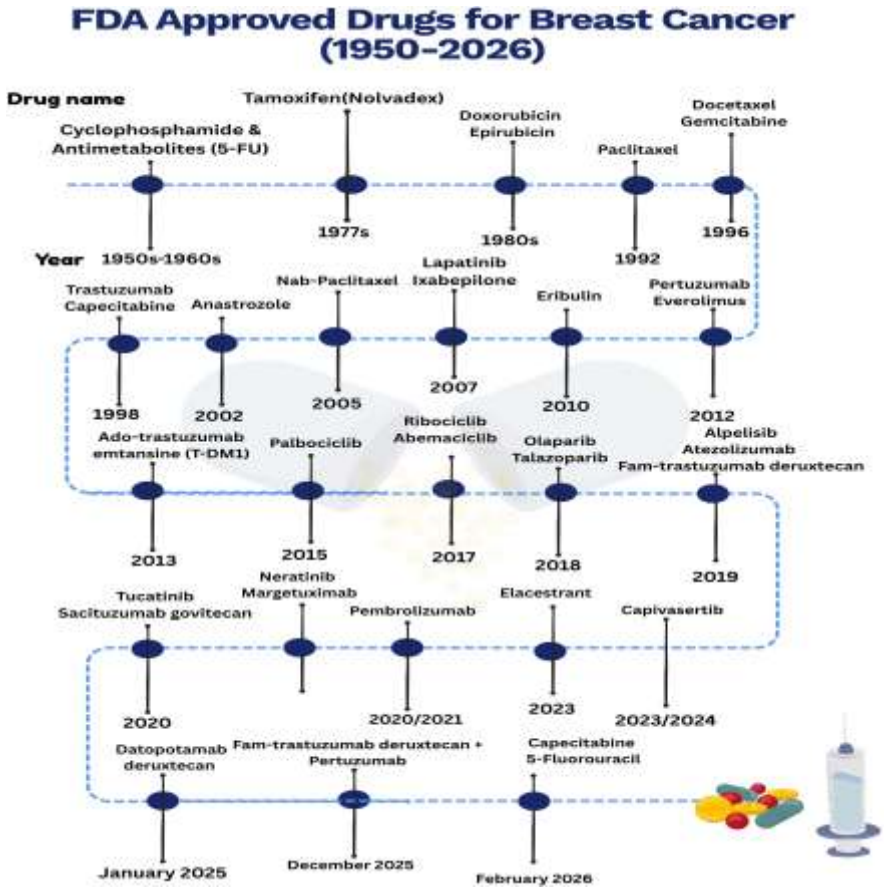

FIGURE 5

FDA approved drugs against breast cancer. In the provided figure we have compiled the drugs approved by FDA starting from year 1950s to the recent one's i.e. 2026. These drugs belong to different classes i.e. small molecule-based chemotherapeutics, small molecule-based targeted therapies (kinase/mTOR inhibitors, etc.), monoclonal antibodies-based drugs, therapies targeting hormones, and more.[14]

2. Structural characteristics

The structural architecture of benzothiazole imparts upon it a unique blend of chemical properties, making it an attractive scaffold for drug design. The benzene ring provides aromaticity and hydrophobicity, crucial for ligand-receptor interactions, while the thiazole ring contributes to the heterocyclic moiety, conferring specific pharmacological activities. The presence of nitrogen and sulfur atoms within the thiazole ring further enhances the electron density and polarity of benzothiazole derivatives, influencing their binding affinity and bioavailability.[4] Moreover, the positional substitution patterns on the benzene and thiazole rings significantly influence the physicochemical properties and biological activities of benzothiazole derivatives. Substitutions at different positions alter the steric hindrance, electronic distribution, and lipophilicity, thereby modulating their pharmacokinetic and pharmacodynamic profiles. This structural diversity enables the rational design and optimization of benzothiazole-based compounds with tailored properties for specific therapeutic applications[15]

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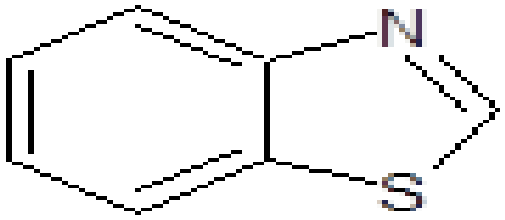


Fig. no. 6 : Structure of benzthiazole.[16]

In recent years, advances in synthetic methodologies, combinatorial chemistry, and computational modelling techniques have further propelled the exploration of benzothiazole derivatives in drug discovery. The advent of high-throughput screening platforms and virtual screening approaches has accelerated the identification of lead compounds with desirable pharmacological properties. Moreover, the development of prodrugs and formulation strategies has addressed challenges related to bioavailability and tissue-targeting, enhancing the clinical translation of benzothiazole-based therapeutics.[17]

3. Role in drug Discovery and Development

Benzothiazole derivatives have emerged as valuable pharmacophores in drug discovery and development, with numerous compounds demonstrating promising therapeutic potential across various disease areas. The multifaceted biological activities exhibited by benzothiazole derivatives, including anticancer, antimicrobial, anti-inflammatory, and antiviral effects, underscore their significance as versatile therapeutic agents. Furthermore, the synthetic accessibility and modifiability of benzothiazole scaffold have facilitated the exploration of structure-activity relationships (SAR), guiding the rational design of novel compounds with enhanced potency and selectivity[18]

4. Drug Design and Development

The structural versatility of benzothiazole scaffold offers ample opportunities for rational drug design and optimization. Structure-activity relationship (SAR) studies have elucidated key structural features essential for pharmacological activity, guiding the design of potent and selective benzothiazole-based drugs. Moreover, computational modelling techniques, such as molecular docking and quantitative structure-activity relationship (QSAR) analysis, have facilitated the rational design of novel benzothiazole derivatives with improved pharmacokinetic and pharmacodynamics properties. Furthermore, the development of prodrugs and drug delivery systems has enhanced the bioavailability and tissue-targeting capabilities of benzothiazole-based therapeutics, thereby expanding their clinical utility.[19]

5. Structure-activity relationship (SAR) studies

SAR studies play a pivotal role in guiding the rational design and optimization of benzothiazole-based drugs. By systematically modifying the chemical structure of benzothiazole derivatives and evaluating their pharmacological activities, researchers can elucidate the key structural features essential for biological potency, selectivity, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties[20]

6. Quantitative Structure-Activity Relationship (QSAR) Analysis:

QSAR analysis involves the development of mathematical models correlating the chemical structure of benzothiazole derivatives with their biological activities. QSAR models quantify the relationship between structural descriptors (e.g., molecular size, lipophilicity, electronic properties) and pharmacological endpoints, facilitating the

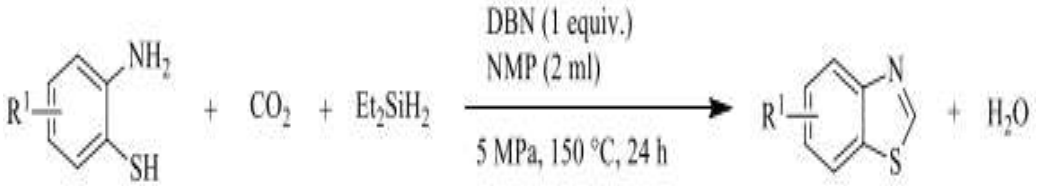
prediction of the activity of novel compounds and the optimization of molecular properties.[21]

7. Synthesis of benzothiazole: [22]

7.1. Cyclization reaction

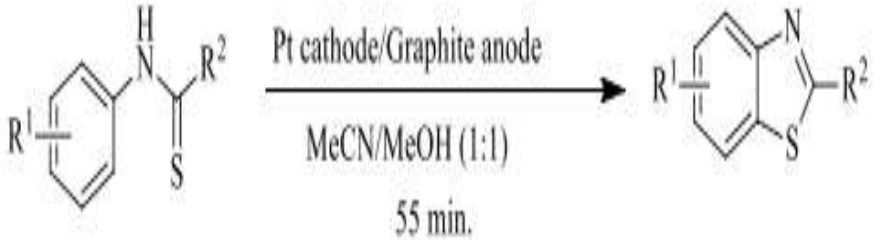
a. Cyclization of co_2 as raw material

The DBN catalysed synthesis of benzothiazoles from 2- aminothiophenols and CO2 via cyclization reaction in the presence of diethyl silane. Many benzothiazole derivatives were afforded in excellent yields. This work demonstrates that hydro silane played a crucial role in the preparation of benzothiazoles and successfully avoided the formation of benzothiazolines as by-products. This method gives an ecofriendly path for synthesizing benzothiazoles and their derivative.

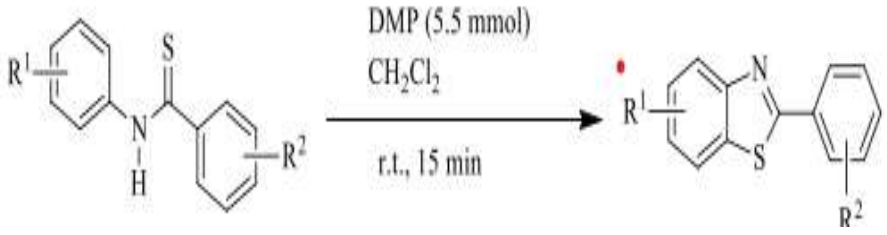


b. Cyclization of various substituted thioamides

In order to create moderate to good yield and high current performances from aryl thioamides, the supporting electrolyte-free electrochemical and catalyst-free synthesis of benzothiazoles utilizes a flow electrochemical reactor. The described methods for producing benzothiazoles in this technique were greatly improved by the straightforward scaling up of the reaction.

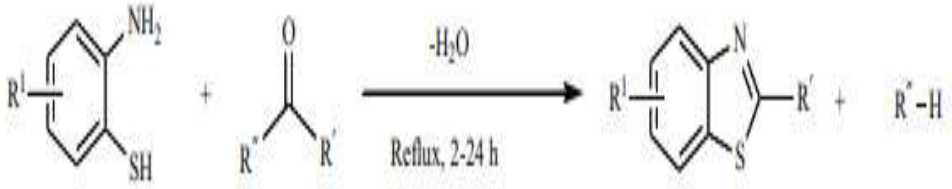


The cyclization method used to create benzothiazoles from sulfamide substrates. DMP was used as the catalyst while dichloromethane served as the reaction solvent during the reaction, which was conducted at room temperature. The method reveals that the novel oxidized benzothiazole chemical is produced in high yields by a thiol radical and that solid-phase synthesis is also capable of synthesizing combinatorial libraries of heterocycles. With this strategy, you may benefit from short reaction times, high activity levels, high yields, and gentle reaction conditions.



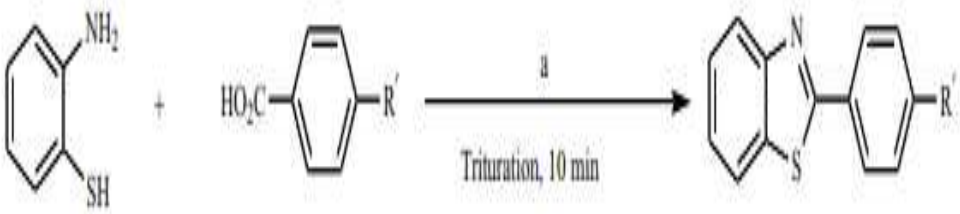
7.2. Synthesis of benzothiazole by condensation reaction [23]

a. Condensation of 2-amionbenzenthiol with aldehyde



In the presence of acacia concinna as a biocatalyst, the microwave radiation accelerated the synthesis of 2-aryl-benzothiazoles from various types of aryl aldehydes and 2-aminothiophenol. The current technique differs from the conventional method in that it is more ecologically friendly, requires less reaction time, is solvent-free, and produces great yields of the required compounds

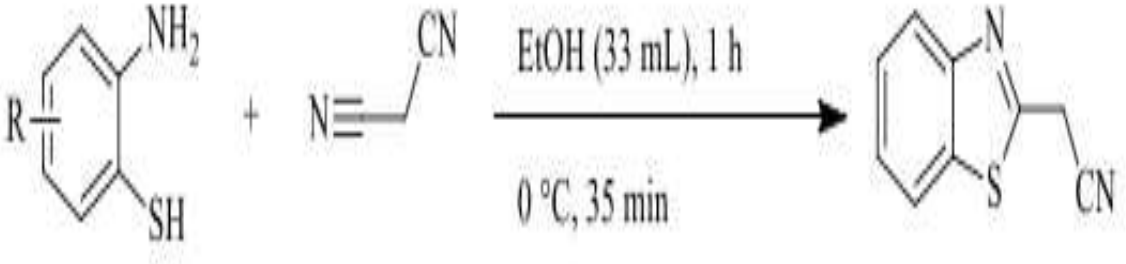
b. Condensation of 2-amionbenzenthizole with acid



molecular iodine was utilized to achieve a highly economical and good yield of benzothiazole derivatives in a one-pot, solvent-free, and solid-phase condensation of ortho-amino thiophenol with benzoic acid derivatives for 10 minutes. The novel approach significantly reduces cost by 17-fold when compared to polyphosphoric acid and Br catalysed microwave synthesis because no additional chemicals or solvents are required for the reaction. The benefits of using iodine are that it is nonselective, low-priced, requires a shorter reaction time, and can be carried out under solvent free conditions

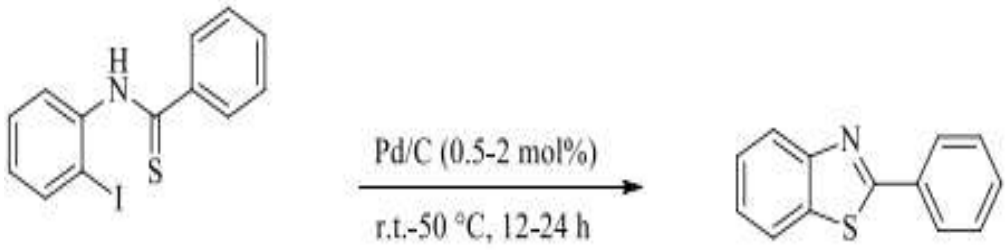
c. Condensation of 2-aminobenzenthizole with nitrile[24]

synthesized 2-cyanomethyl benzothiazole via condensation of ortho-amino thiophenol with malonodinitrile in the presence of glacial acetic acid. In the subsequent step, conc. HCl was added dropwise to a mixture of 2-cyanomethyl benzothiazole in isopropanol and water for the formation of 2-benzothiazolylcyanoxime, which is a strong multidentate ligand for chemical coordination

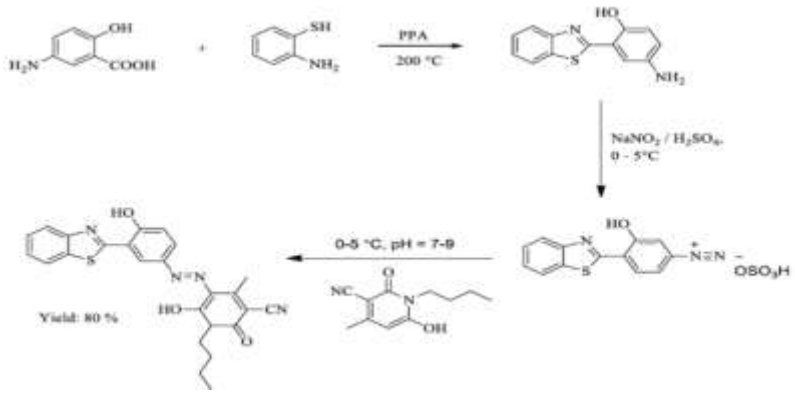


7.3. Other methods [25]

a. 2-substituted benzothiazoles were produced by cyclizing o-iodothiobenzanilide derivatives at room temperature using Pd/C as the catalyst. The method requires very mild conditions, is high yielding, additive-free, and ligand-free.



b. The intermediate is created by cyclizing 5-aminosalisycyclic acid with 2-aminothiophenol to create new azo conjugated benzothiazole dyes. The intermediate was treated with concentrated H2SO4 and sodium nitrite (NaNO2) at 0–5 °C, and then coupled with compound at 0–5 °C while maintaining a pH of 7-9, to produce the diazonium salt solution. High yields of the anticipated new heterocyclic dyes were produced through effective synthesis



7.4. Other synthetic strategies[26]

a. Oxidative cyclization: Oxidative cyclization reactions involve the oxidation of thioanilines or thioamides to form benzothiazole derivatives under oxidative conditions, typically using oxidants such as iodine or hydrogen peroxide.

b. Ring-Opening reactions: Ring-opening reactions of cyclic sulfonamides or cyclic sulfides followed by cyclization can be employed to access benzothiazole derivatives with fused ring systems.

c. Microwave-Assisted synthesis: Microwave irradiation can accelerate the synthesis of benzothiazole derivatives by facilitating reaction kinetics and promoting higher yields in shorter reaction times compared to conventional heating methods.

d. Solid-Phase synthesis: Solid-phase synthesis strategies involve the immobilization of starting materials on a solid support, enabling the synthesis of benzothiazole derivatives through iterative coupling and cyclization reactions, followed by resin cleavage and product isolation.

8.Pharmacological activities of benzothiazole[27]

8.1. Anti-cancer activity:

Intensive research on benzothiazole ring system is going on to identify novel lead compounds to fight against different cancers, and few recent trends in

this field are briefly explained to understand the anticancer potential of Benzothiazole derivatives by assessing the effects of various substitution. The role of benzothiazole moiety in oncology was assessed during the development and screening of tyrosine kinase inhibitors during the late 20th century. In the year of 1994, Stevens *et al*. synthesized a series of 2-phenylbenzothiazoles derivatives bearing polyhydroxy groups and screened them against various cancer cell lines (MCF-7, Colon cancer and squamous carcinoma cell lines) which overexpress the Epidermal Growth Factor Receptor (EGFR) to assess the activity of compounds against tyrosine kinase receptor. Simultaneously, they computed the estrogen activity of benzothiazole derivatives as they were found as the structural analogues of 2-phenylindoles. The synthesized compounds had shown significant and selective cytotoxicity against breast cancer cell line (MCF-7) and it concluded that the antitumor activity of compounds is not allied with tyrosine kinase receptors

8.2. Anti-convulsant activity:

N-(6-methoxybenzothiazol-2-yl)-4-oxo-4-phenylbutanamide a valuable pharmacophore in the investigation of agents controlling seizures and intoxication in epilepsy. This compound, after administration, improved the GABA level substantially and also decreased the development of ACR mediated neurotoxicity. There is also a need for more molecular and clinical research to establish its efficacy and mode of action during epilepsy. And many of benzothiazole derivative shows anti-convulsant activity.

8.3.Anti-inflammatory activity:

The ability of several types of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] Thoi]-1 H - benzimidazoles, benzothiazoles, and benzoxazoles to inhibit human enzyme cycloxygenase-2 (COX-2) was investigated. 2-(4'- butyl-3',5'-dimethylpyrazol-1'-yl)-6-substituted benzothiazole and 4-butyl-1-(6'-susbtituted-2'-benzothiazolyl)-3- methylpyrazol-5-ones and were found to display significant anti-inflammatory activity.

8.4. Anti-tubercular activity: [28]

For anti-tubercular efficacy, 2(Substituted Aryl Amino)-5, 6- disubstituted/6-substituted (1, 3) benzothiazoles are used.

8.5. Local anaesthetic:

alkyl/aryl amino propionyl 2-amino benzothiazole and 2-amino (substituted) benzothiazole and 2-(alkylamino acyl imino) 3-methyl benzothiazolines shows local anaesthetic activity.

8.6. Cardiovascular agent:

Synthesis of amino derivatives of 4, 5, 6, 7-tetrahydro benzothiazoles for cardiovascular activity. substituted 2-phenyl benzothiazoles for calcium channel blocking activity.

8.7. Enzyme inhibitor:

Sulphonamide benzothiazole derivatives as topical carbonic anhydrase inhibitors. benzothiazole hydroxy urease as inhibitors of 5-lipoxygenase enzyme. The development of Triticum aestivum is controlled by synthetic 3-(2-alkoxy carbonyl-ethyl)-2-benzothiazolinones.

8.8. Anti-oxidant activity:

The ability of an antioxidant to capture free radicals is its primary quality. In biological systems, there are a multitude of sources of highly reactive free radicals and oxygen species. These free radicals can cause degenerative diseases and can oxidize proteins, lipids, nucleic acids, or DNA. Since phenolic acids, polyphenols, and flavonoids scavenge free radicals such peroxide, hydroperoxide, and lipid peroxyl, they prevent the

oxidative processes that cause degenerative illnesses. According to several clinical trials, the antioxidants found in fruits, vegetables, tea, and red wine are the primary reasons for these foods' effectiveness in lowering the prevalence of chronic diseases like heart disease and some malignancies. Miller and Rigelhof have extensively researched and reported on the free radical scavenging properties of antioxidants in food. Numerous antioxidants, both natural and synthetic,

8.9. Anti-diabetic activity: [29]

Diabetes mellitus is a group of metabolic ailments distinguished by high blood sugar rising from defects in insulin secretion, insulin action, or both The eyes, kidneys, nerves, heart, and blood arteries are among the many organs whose long-term damage, abnormalities, and failure are linked to the chronic hyperglycaemia of diabetes. Various infective steps are involved in the development of diabetes. This ranges from autoimmune destruction of the β-cells of the pancreas with resulting insulin scarcity to irregularities that result in opposition to insulin action. The basis of the irregularities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action effect from insufficient insulin discharge and/or decreased tissue acknowledgement to insulin at added points in the complex pathways of hormone action. When two abnormalities coexist in the same patient, such as deterioration of insulin discharge or defects in insulin action, it is usually difficult to determine which one, if either

8.10. Antimicrobial activity

Benzothiazole derivatives exhibit potent antimicrobial activity against a wide range of bacterial, fungal, and parasitic pathogens. The antimicrobial effects of benzothiazoles are attributed to their ability to disrupt essential cellular processes or structures in microorganisms, including cell wall synthesis, protein synthesis, and membrane integrity.

8.11. Antibacterial activity:

Benzothiazole derivatives such as ciprofloxacin and levofloxacin are fluoroquinolone antibiotics that inhibit bacterial DNA gyrase and topoisomerase IV, leading to the inhibition of DNA replication and cell division. These compounds are effective against both Gram-positive and Gram-negative bacteria, making them valuable agents for the treatment of bacterial infections.

8.12. Antifungal activity:

Benzothiazole derivatives like clotrimazole and miconazole are imidazole antifungal agents that inhibit the synthesis of ergosterol, a key component of fungal cell membranes. By disrupting membrane integrity, these compounds exert fungicidal effects against various fungal pathogens, including Candida species and dermatophytes.

9. Molecular Docking Study:[30]

Following successful synthesis of suggested compounds, their reactions and chemistries with the EGFR are studied using Molecular Docking. Molecular docking of molecules in the three-dimensional in nature X-ray structure of the EGFR (2xkw) was performed with the Molecular Designing Suite (MDS) software tool (v. 3. 5). The protein-protein ligand complex was built using X-ray structure of proteins supplied from the Protein Data Bank (PDB). [10] All compounds were created using Chemistry Draw Ultra v.8.0 and minimized with the Merck Molecular Pressure Field. The docking investigation was carried out on a three-dimensional representation of the catalytic location of the aforementioned proteins, with the program parameters set to their default levels. A genetic method developed for MDS has been succesfully used to dock inhibitor into the catalytic

sites of enzymes. The resulting bind score (Dock score) represents the molecules' binding energies in KJ/mole, with a smaller dock score indicating a greater affinity for the receptor.

10. Molecular Docking Study:

The docking score of all prepared compounds by docking study were calculated[16] and are shown in Table 2. The synthesized molecules have shown lowest binding energy scores which are indicates the maximum interaction of molecules with receptor.

Table 3 summarizes the many types of interactions that occur with the receptor, as well as the binding energy (Dock score) determined from molecular docking study of selected compounds.

Figure 2. depicts several interactions between manufactured compounds and amino acid residues found in the active site of EGFR.[31]

Table 1: Docking score and various interactions of selected ligands

Ligands	Types of interactions				Dock score (Energy in kj/mole)
	Hydrogen bonding	Hydrophobic	Van der waals	Charge	
A1	++	-	++++	-	-5.1264
A2	+	+++	++++	-	-4.5243
A3	++	+	++++	-	-7.6439
A4	+	-	++	-	3. 5452

+++: The active location of EGFR has an average amount of amino acid residues.
++: a small amount of amino acid residues are found in the active region of EGFR.
- -: No amino acids substitutions in the active location of EGFR.

Fig. 7: RTK domain bound to ligand in to the active site of EGFR [32]

CONCLUSION

Breast cancer until today remains a significant global health threat characterized by multifaceted and complex etiology and diverse clinical presentation. This comprehensive review examines the evolving dynamic landscape of breast cancer research, pointing out the complexity of the disease and strategies implemented to tackle it. Firstly, we discussed the epidemiology and various risk factors such as genetic mutations (BRCA1/2, TP53, PTEN), hormonal influences, several lifestyle risk factors (obesity,smoking, etc.), Benzothiazoles are fused membered rings, which contain heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Benzothiazole is an interesting pharmacophore exhibiting diverse pharmacological activities like antimicrobial, anticancer, anthelminthic, antidiabetic, antitubercular, anticonvulsant, antioxidant, anti-inflammatory, antifungal, antipsychotic etc. The present article extensively covers various procedures of synthesis of 2-substituted benzothiazole core and its analogues – by utilizing distinctive catalysts, solvent conditions, reactants immobilized on solid support and microwave irradiation. Variations in synthetic procedures are studied to explore chemo-selectivity of the reactions, in-expensive, eco-friendly, less time-consuming procedure with easy and quick isolation of the products. Ongoing clinical trials of different benzothiazole derivatives, exploring additional pharmacological activities, are also included.

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