WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 10, 284-291. Review Article ISSN 2277–7105

A PERSPECTIVE ON SYNTHESIS OF NOVEL BENZOTHIAZOLE DERIVATIVES BY USING MICROWAVE-ASSISTED & CONVENTIONAL TECHNIQUES

Aniqua T. S. Sheikh[1]*, D. P. Kawade[2], Ashwin U. Rahangdale[3] and Anirudh S. Mishra[4]

Department of Pharmaceutical Chemistry, Priyadarshini J.L College of Pharmacy, Nagpur, Maharashtra, India.

Article Received on
27 March 2024,

Revised on 17 April 2024,
Accepted on 07 May 2024

DOI: 10.20959/wjpr202410-32365

***Corresponding Author**
Aniqua T. S. Sheikh
Department of Pharmaceutical Chemistry, Priyadarshini J.L College of Pharmacy, Nagpur, Maharashtra, India.

ABSTRACT

Benzothiazole refers to a pair of rings that include the heterocycles thiazole and benzene combined. Benzothiazole-based compounds have been developed for use as anti-tubercular, anti-diabetic, anti-cancer, antibacterial, antifungal, anti-inflammatory, analgesic, anti-HIV, anti-oxidant, anti-convulsant, anti-malarial, and other medicinal agents throughout the entire field of medicinal chemistry. This work offers a logical and comprehensive assessment of these advancements. This work focuses on utilizing a one-pot, three-component microwave aided approach to synthesize novel substitutions of ethyl 2-methyl4-(pyridine-2-yl)-4H-benzo [4,5] thiazolo [3,2-a]pyrimidine-3-carboxylate. Benzothiazole derivatives with polyfunctionalized tri-heterocyclic structure have recently been synthesized and described by means of several spectroscopic methods, such as single crystal X-ray analysis, FT-IR, 1H NMR, and 13C NMR, in addition to elemental analysis. Each final scaffold's antibacterial and antitubercular efficacy against Mycobacterium tuberculosis H37RV was tested.

KEYWORDS: Benzothiazole, antibacterial, antifungal, microwave-assisted, solvent-free condition, etc.

INTRODUCTION

The sulfur atom is where the thiazole moiety's numbering begins. Four or five thiazole sites fused form the fundamental structure of benzothiazole. The thiazole ring has five members, and each ring has one atom of nitrogen and one of sulphur.[1,2,3] Combining two rings with the

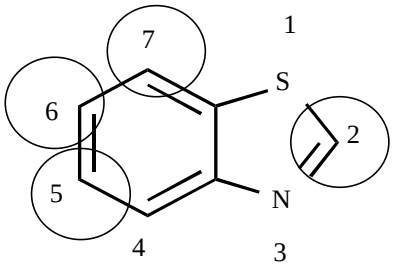
heterocycles thiazole and benzene results in benzothiazole. Thiazole and its physiologically and pharmacologically active derivatives have a core structure that is attributed to the ring's sulfur and nitrogen atoms. Thiazole and its physiologically and pharmacologically active derivatives have a core structure that is attributed to the ring's sulfur and nitrogen atoms.[7] Benzothiazole derivatives are used in many areas of chemical study since they are heterocyclic molecules. Environmental risks in synthetic processes are mostly caused by the use of hazardous solvent media, multiple-step reactions, and toxic metal catalysts. To circumvent the aforementioned circumstances and employ environmentally friendly reagents, appealing tactics in synthetic research include the use of green solvents, and reusable catalysts, avoiding non-biodegradable components, controlling multiple steps, and employing an iterative process.[7,10] In addition to the green chemistry perspective, recyclable catalysts are crucial in preventing bulk catalyst usage and maintaining economies of scale in multicomponent synthetic pathways.[13, 14, 15]

The benzothiazole moiety also garnered a lot of interest as an anticonvulsant agent. A thorough investigation conducted by numerous researchers revealed the key characteristics of benzothiazole derivatives that are essential for their activity, including a distal hydrophobic occupied group, an electron donor pair, and a hydrogen binding domain. This review paper is anticipated to be beneficial for fresh ideas in the search for more logical formulations of BTA-based medications that are more potent and less hazardous, as well as more efficient pathologic probes and diagnostic agents.[16] Because of its ability to bind amyloid, benzothiazole, particularly Benzothiazoles with 2-aryl, are powerful radioactive imaging agents in neurological diseases.

Much work has lately been devoted to the development of novel and highly successful synthetic techniques, include multicomponent coupling protocols, transition metal-catalyzed cyclization, and [3 + 2] cycloadditions, in order to produce derivatives of benzothiazole. MCRs are a powerful ecologically friendly alternative to conventional synthesis; yet, they are affected by microwave and solvent-free conditions. Biginelli reaction is a well-known multicomponent process for the creation of related poly-heterocycles and 4H-pyrimido [2,1-b]benzothiazoles. This strategy's primary benefits include ease of use, simplicity in operation, convergence, quick reaction times, high atom economy, ease of setup, moderate reaction conditions, and ecologically safe settings.[17]

In 1893, Biginelli reported the first example of 3,4-dihydropyridine-2-(1H)one is created by one-pot three-component condensation process using urea, β-ketoesters, and aldehyde. Derivatives of chemical 2-amino benzothiazoles and instead of urea, 2-amino benzimidazoles are utilized. Employing PdCl2 as a potent catalyst, a solvent-free reaction involving ethyl acetoacetate, pyridine 2-aldehyde, and many 2-amino-benzothiazole derivatives were carried out using a microwave. This procedure was an effective ethyl synthesis from three components in one pot 2H-benzo-2-methyl-4-(pyridine-2-yl).[4,5] Thiazolo [3,2-a] derivatives containing pyrimidine-3-carboxylate, yielding fresh themes in the structure with promise bioactivity. Compounds demonstrate antibacterial and antitubercular properties against both gram-positive and gram-negative bacterial strains, as well as Mycobacterium TB H37RV.[17, 18, 20]

Physicochemical characteristics of benzothiazole



- **Formula:** C_7H_5NS
- **Molecular Mass:** 135.1863 g/mol
- **IUPAC Name:** 1,3-Benzothiazole
- **Appearance:** Yellow liquid
- **Density:** 1.24 g/cm³
- **Boiling point:** 441–442 °F (500–501 K) or 227–228 °C.
- **Solubility:** In ethanol, ether and water
- **Melting point:** 36 °F (2 °C; 275 K)
- **Log P:** 2.01

Thiazole and its equivalents, like benzothiazole, are crucial because they serve as a model for the creation of amazing thiazole derivatives with diverse pharmacological activities that are helpful in the treatment of a range of illnesses. Benzothiazole is crucial since it serves as a model for the creation of amazing derivatives that have diverse pharmacological properties and can be used to treat a range of illnesses.[18] Environmental risks in synthetic processes are mostly caused by the use of hazardous solvent media, multiple-step reactions, and toxic metal catalysts. The use of environmentally friendly reagents, the use of green solvents, reusable catalysts, non-biodegradable components, multistep control, and an iterative approach are all desirable tactics in synthetic research to avoid the aforementioned situations. Here, benzothiazole-tethered pyranopyrazole derivatives were made under conditions that were good for the environment: an eco-friendly catalyst, a combination of ethanol and water as a

solvent, a single pot, an atom, and step economy conditions. There was an excellent product yield.[20]

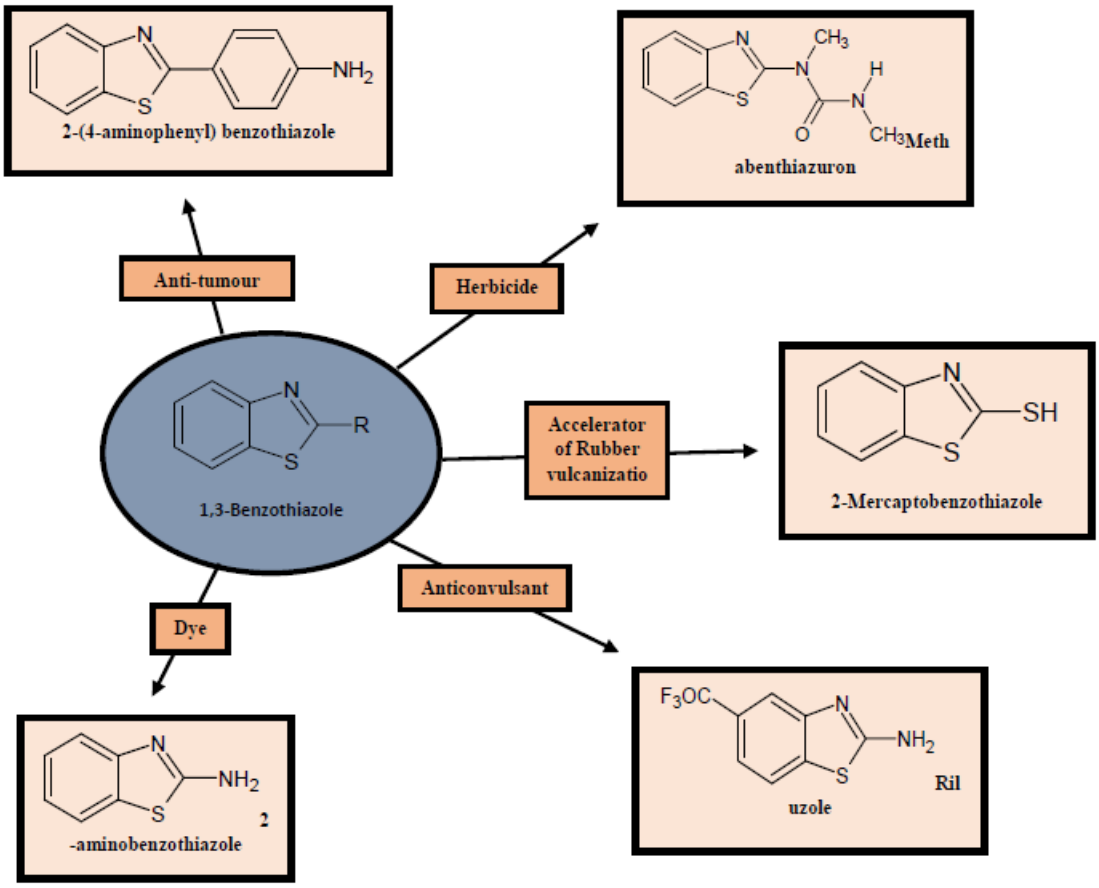
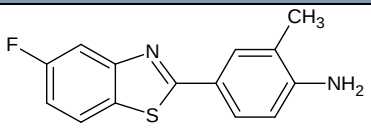
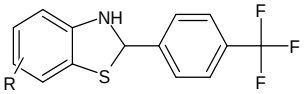
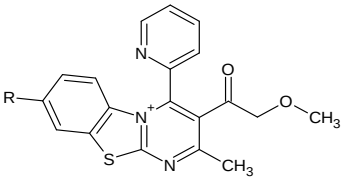
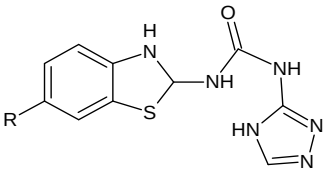
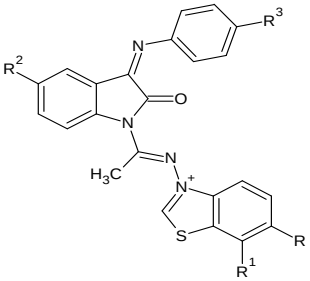
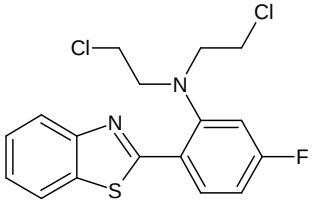


Fig.2: Benzothiazole, nucleus of various compounds having multiple activities.

Therapeutic Potential of Benzothiazole.

Sr. no.	Authors	Compounds	Activity
01.	**Mohmoud al Talib.**	 4- (2-methylaniline-5-(5-fluoro-1,3-benzothiazol-2-yl)	**Antimicrobial activity** and **Antibacterial activity** against staphylococcus aureus, and candida albicans.
02.	**C. Praveen et al.**	 2,3-dihydro-1,3-benzothiazole-2-[4-trifluoromethyl)phenyl	**Analgesic activity**

03.	**Manoj N. Bhoi et al.**	 3-pyrimido[2,1-b]–(Methoxyacetyl)-2-methyl-4-(pyridin-2-yl)[1,3]Benzothiazole	**Antitubercular activity** against mycobacterium tuberculosis
04.	**Qazi Yasar et al.**	 1. (Dihydro-1,3-benzothiazol-2-yl)the urea -3-(4H-1,2,4-triazol-3-yl)	**Anti-convulsant activity**
05.	**Raja Reddy and Murthy et al.**	 3-({(1)-1-[(3)-2-oxo-3-(phenylimino)-2,3-dihydro-1H-indol-1-yl]ethylidene}amino)-1,3-benzothiazole	**Anti-helmintic Activity**
06.	**Kini S et al.**	 N,N-bis(2-chloroethyl)-5-fluoroaniline 2-(1,3Benzothiazol-2-yl)	**Anti-cancer Activity**

Benzothiazole moieties are present in compounds involving biological functions like anthelmintic, antibacterial, anticancer, anti-diabetic effects. They are also used in industry as antioxidants and vulcanization accelerators. In the past 10 years, the preferred the idea of structure-activity has gained popularity in medicinal chemistry and shown to be a successful approach for the discovery of new drugs.[22] Because of their intrinsic affinity for a number of biological receptors, benzothiazoles are the model structures. They are a perfect supply comprising core scaffolds and pieces of capping for the timely creation and amalgamation of particular compounds frame. Benzothiazole, a significant heterocyclic compound, a weak base, and it continues to be highly interesting to scientists.

Compared to conventional methods for organic synthesis, organic electrosynthesis is a safer and more environmentally friendly process that uses less energy. One special type of bicyclic ring system is benzothiazole. The synthesis of this molecule is of tremendous interest because of its powerful and profound biological actions, which make it of major medicinal value. Compounds used in research to assess novel goods with intriguing properties contain the tiny, straightforward benzothiazole nucleus.[23]

Since infectious diseases have higher rates of death, morbidity, and treatment costs, antimicrobial resistance (AMR) is a global concern. Of the 32 antibiotics that were tested in clinical trials, only six were deemed to be novel and to possess a unique moiety, as per the WHO 2019 report. The rest of this list's antibiotics have previously been identified as moiety (WHO AMR 2019). To combat resistance issues, it is essential to create new antibiotics.[24] Antimicrobial drug resistance, or AMR, poses a noteworthy risk to the healthcare system regarding cost, morbidity, and death. Multi-drug-resistant microbe issues have gotten alarmingly worse in many nations worldwide in recent decades. Information gleaned from several publications demonstrated how the benzothiazole moiety and its derivatives may contribute to the production of the unusual and important lead chemical.

MATERIAL AND METHODS

A. Microwave-assisted method

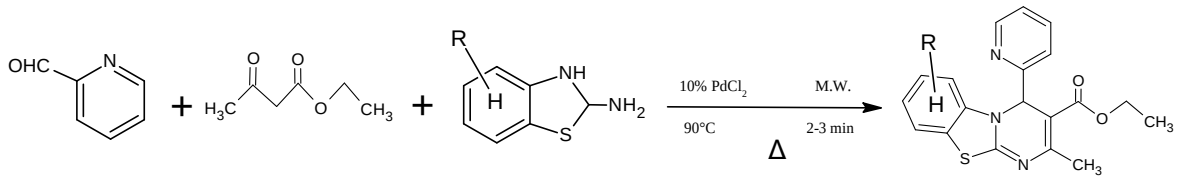
A combination of b-diketone, such as ethyl acetoacetate (4.668 mmol), pyridine 2-aldehydes (4.668 mmol), and derivatives of 2-amino benzothiazole (4.668 mmol) were placed in a 10 ml round bottom flask. Then heated for 2–5 minutes at 90˚C without solvent utilizing $PdCl_2$ (10 mol %) as a catalyst. The reaction mixture was solubilized in ethanol, after allowing to reach room temperature, add to ice water. After filtering the precipitate, ethyl acetate: n-hexane (20 % (v/v)) was used as an eluent in column chromatography to produce ethyl-(substituted)-2-methyl-4- (pyridine-2-yl).

B. Conventional method

A 25 ml RBF was filled with the same chemical mixture, following the same process as previously stated. After mixing, placed in oil bath at 90℃, for 20–70 min in solvent-free environment, with $PdCl_2$ (10 mol%) serving as a catalyst. The concoction of reactions was dissolved in ethanol solvent and brought down to room temperature, then emptied into cold water after each reaction was validated using TLC. The product was filtered repeatedly

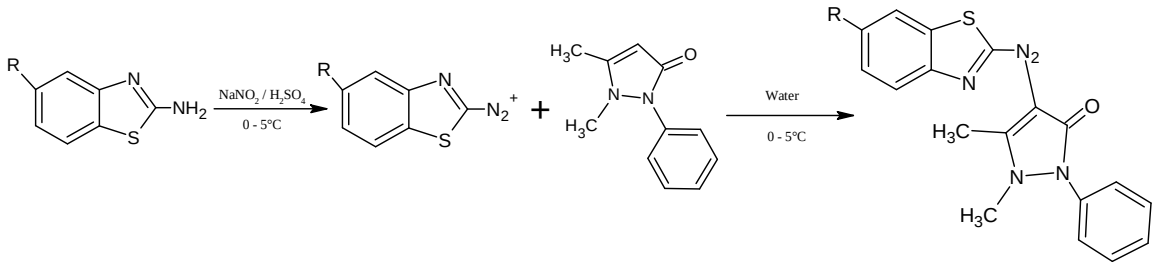
before being added to water. Using column chromatography and an eluent solvent solution (20 % ethyl acetate: hexane), the solid product was easily purified.

Synthetic Schemes



R= NO2, Cl, Me

Scheme-1: Method for synthesizing title compounds in a solvent-free environment.



R= Cl, OC_2H_5 ww

Scheme-2: The process by which azo dyes based benzothiazole analogues are made chemically.

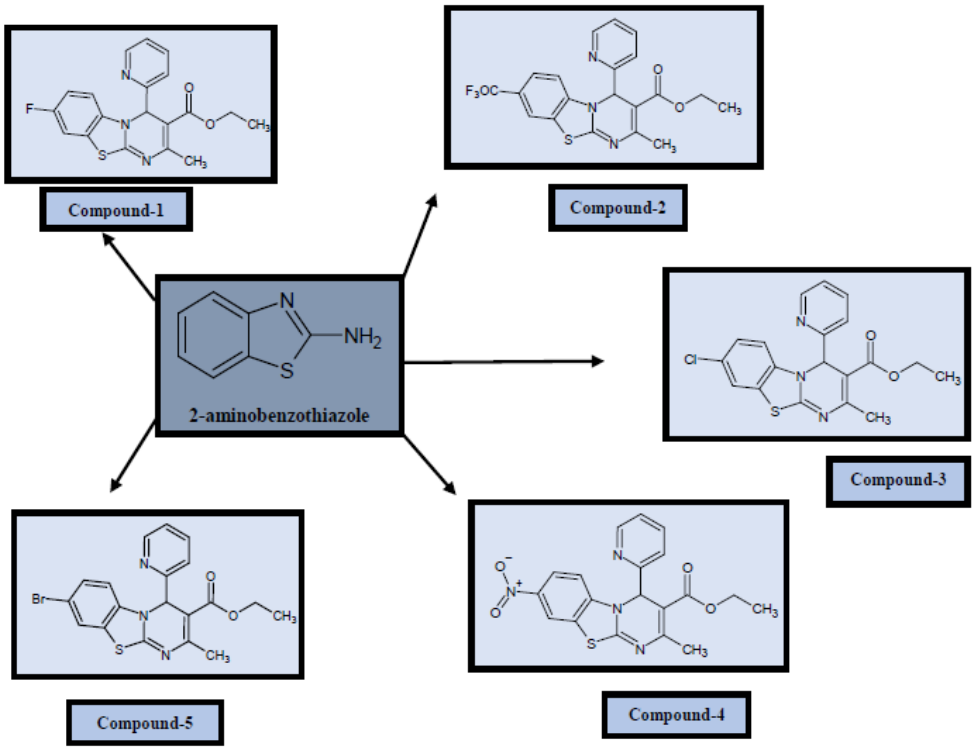
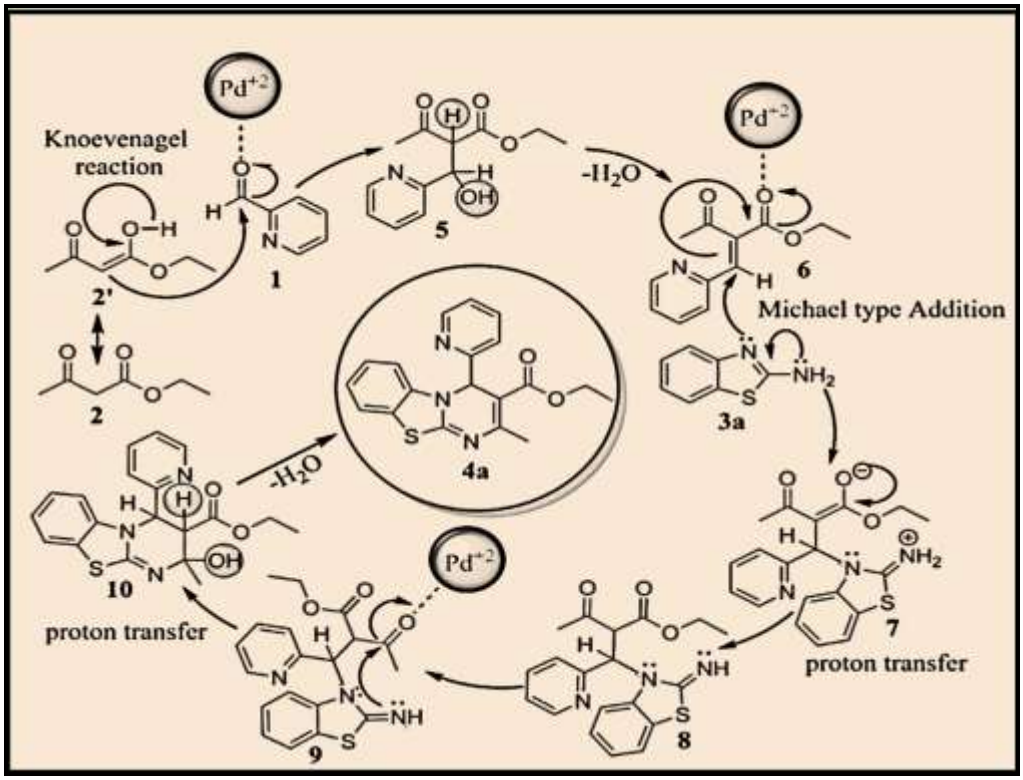


Fig.4: Derivatives of 2-aminobenzothiazole.



Scheme-2: A process for producing 4H-pyrimido[2,1-b]benzothiazoles 4a.

CONCLUSION

Utilizing PdCl2 as a quick catalyst in solvent-free, microwave-assisted circumstances, to create ethyl 2-methyl4-(pyridine-2-yl)-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate derivatives. A new, effective, one-pot synthesis of three-components involving 2-aldehyde pyridine, ethyl acetoacetate, 2-amino benzothiazole derivatives was disclosed. It's an intriguing method because of the reaction's straightforward one-pot nature. The primary benefits of the new methodology are its novelty, favorable yields, simple setup, cursory automation, and lack of anhydrous conditions. Conditions without solvents, they are much more environment friendly, nontoxic, and safe, were used to conduct the reactions. In addition, the presence of three distinct and significant heterocyclic moieties in a single molecule—pyridine, pyrimidine, and benzothiazole rings—is remarkable due to the potential uses of these derivatives in pharmacological and biological contexts.