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REVIEW ON 2-SUBSTITUTED BENZOTHAZOLES: DIVERSITY OF SYNTHETIC METHODS AND BIOLOGICAL ACTIVITIES

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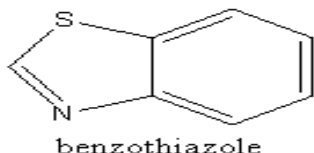
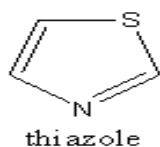
ABSTRACT: In recent years heterocyclic compounds analogues and derivatives have attracted wide attention due to their useful biological and pharmacological properties. Benzothiazole is a privileged bicyclic ring system with diverse applications. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as anticancer, antimicrobial, and antidiabetic, anticonvulsant, anti-inflammatory, antiviral, ant tubercular activities. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. This review is mainly focus on the research work reported in the recent scientific literature on different biological activities of benzothiazole compounds.

INTRODUCTION: The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design ¹. Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole is a privileged bicyclic ring system.

Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. The small and simple benzothiazole nucleus if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities.

Benzothiazoles are fused member rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter. Thiazole was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889. The numbering in thiazole starts from the sulphur atom. The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole.

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In the 1950s, a number of 2-aminobenzothiazoles were intensively studied, as the 2- amino benzothiazole scaffold is one of privileged structure in medicinal chemistry and reported cytotoxic on cancer cells ². It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering.

Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial ³⁻⁷, anticancer ⁸⁻¹¹, anthelmintic ¹², anti-diabetic ¹³ activities etc, they have also found application in industry as anti-oxidants, vulcanisations, accelerators.

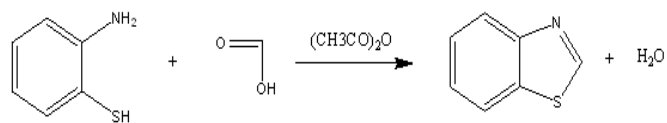
Various benzothiazoles such as 2-substituted benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imaging agents, and anticancer agents. The 2-(4-aminophenyl) benzothiazoles are novel class of potent and selective antitumor agents and display characteristic profile of cytotoxic response across the cell lines. In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties.

In last few years it was reported that benzothiazole, its bioisosters and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacteria's (e.g., *Enterobacter*, *Pseudomonas aeruginosa*, *E. coli*, and *Staphylococcus epidermidis* etc.) and the yeast (e.g., *Candida albicans*).

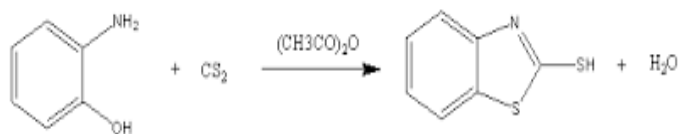
1) Synthetic Methods:

Synthesis of 2-substituted benzothiazole by using acetic anhydride ¹⁴:

Benzothiazole may be prepared by action of acid anhydrides (or) chlorides on o-aminothiophenols and formic acid in presence of acetic anhydride.

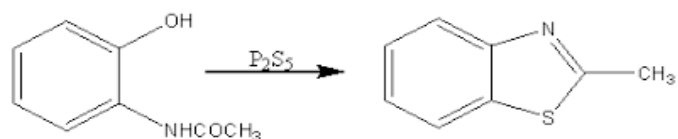


2-mercaptobenzothiazole is vulkanisation accelerator it may be prepared as follows



Synthesis of 2-substituted benzothiazole by using Phosphorus pentasulfide ¹⁵:

Benzothiazoles are also formed by action of phosphorus pentasulfide on o-acylaminophenols.



Synthesis of 2-substituted benzothiazole by using Condensation of o-aminophenol:

O-aminophenol is a versatile starting material for synthesis of different kind of heterocyclic rings. 2-Substituted benzothiazole can easily synthesize by applying condensation with aldehydes and substituted aromatic acids in presence of different catalyst.

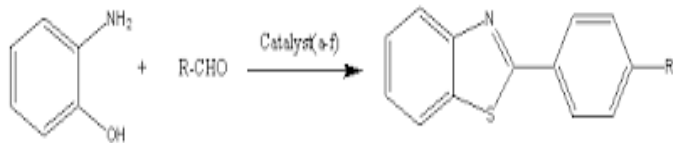
Condensation of o-aminophenol with aldehydes ¹⁶:

Treatment of o-aminophenol with substituted aldehydes affords the synthesis of 2-substituted benzothiazoles using different catalysts and reaction conditions.

Catalysts (a-f):

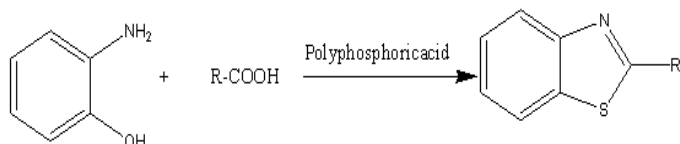
- Montmorillonite, SiO₂/Graphite; Microwave, p-TsOH
- Diethyl bromophosphonate/tert-Butyl hypochlorite, acetonitrile
- Cerium (IV) ammonium nitrate

- d. H₂O₂ /HCl system in ethanol
- e. AcOH /Air, Microwave/ Thermal Heating
- f. Baker's yeast, Dichloro methane



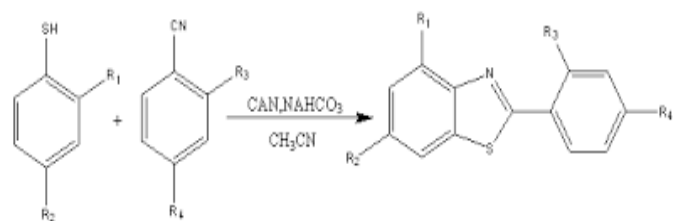
Condensation of o-aminophenol with acids ¹⁶:

Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2- substituted benzothiazoles and gives a good yield ¹⁹.



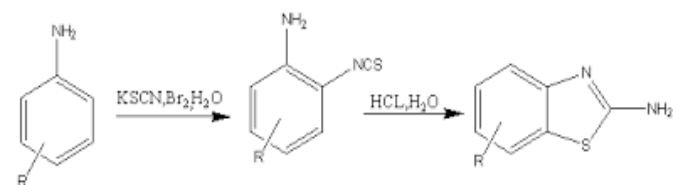
Synthesis of 2-substituted benzothiazole by using coupling method (Coupling between thiophenols and aromatic nitriles) ¹⁶:

Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by ceric ammonium nitrate to give corresponding 2-arylbenzothiazoles in excellent yield.



Synthesis of 2-substituted benzothiazole anilines to synthesized 2-substituted Benzothiazole ¹⁶:

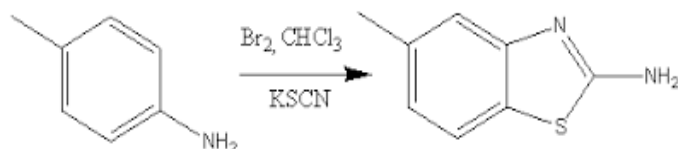
Different substituted anilines when treated with KSCN in presence of glacial acetic acid to synthesize 2-substituted benzothiazole.



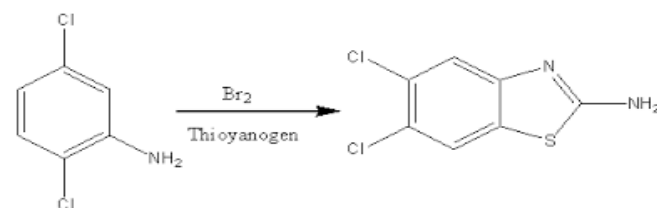
Synthesis of 2-substituted benzothiazole by using different type of catalysts: ^{17, 18}

(i) Bromine as catalyst:

Recently several methods reported which utilize bromine as catalyst. Basically cyclization with bromine achieved by oxidation of aniline, substituted aniline and arylthiourea in acid or chloroform with alkali thiocyanate. 2-aminobenzothiazole and found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2- aminobenzothiazoles.



2-amino-5, 6-dichloro and 2- amino-6, 7- dichlorobenzothiazole by cyclization of suitable substituted aniline with help of thiocyanogen.



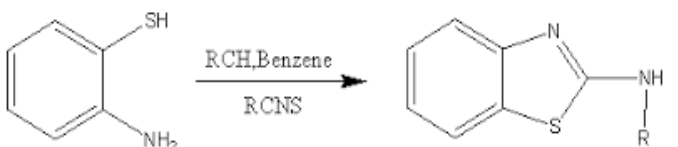
(ii) Sulphuric acid as a catalyst:

Allen used sodium thiocyanate and cyclize p- substituted aniline into 2-amino-6-substituted benzothiazole in the presence of sulphuric acid which act as a catalyst.

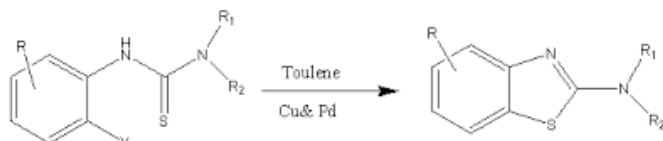


(iii) Benzene as a catalyst:

cyclizations of isothiocyanates to 2-aminobenzothiazole in presence of benzene.

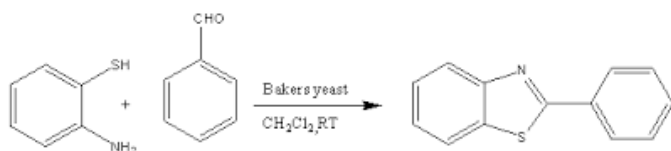


(iv) Copper and palladium-catalyzed cyclization: 2-aminobenzothiazoles through analogous C-S bond forming methodologies. They formed the intramolecular C-S bond with the help of copper- and palladium-catalyzed. Copper- and palladium-catalyzed intramolecular C-S bond formation by cross-coupling between aryl halide and thioureas functionality is demonstrated for the synthesis of 2-aminobenzothiazoles.



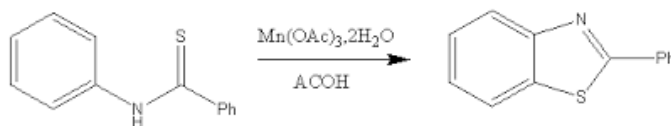
(v) Bakers' yeast to catalyze cyclization:

Employing bakers' yeast to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition.



(vi) Manganese triacetate as a catalyst:

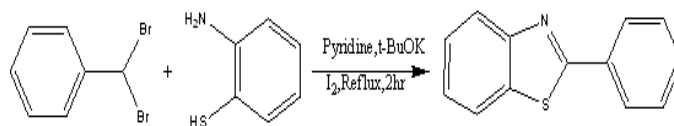
Manganese (III) triacetate is an excellent one-electron oxidant, which has been widely employed to generate free radicals for cyclization reactions. Manganese triacetate is introduced as a new reagent to replace potassium ferricyanide or bromine for radical cyclization of substituted thioformanilides. 2-Substituted benzothiazoles are generated in 6 min under microwave irradiation.



(vii) Pyridine as catalyst:

The synthesis of 2-aryl benzothiazoles from gem-dibromomethylarenes using 2-aminoarylthiols with pyridine is obtained. Benzothiazoles were obtained in high chemical yields under mild conditions. This transformation would facilitate synthesis by short reaction times, large-scale synthesis, easy and

quick isolation of the products, which are the main advantages of this procedure.



(viii) PIFA as catalyst:

A new and general method has been developed for the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates. The method utilizes phenyliodine (III) bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile at room temperature to effect cyclization within 30 min in moderate yields.



2) Pharmacological activities:

The main objective of present is to search for the potent compound for pharmacological activities with lesser adverse effects. Benzothiazoles are established in literature as important biological active heterocyclic compound. These derivatives are the subject of many researches studies due to their wide spread potential biological activities.

Literature survey revealed that benzothiazole derivatives posses diverse biological activities.

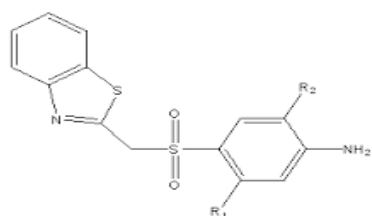
Various pharmacological activities are as follows:

1. Anti tubercular and antidiabetic activity
2. Anti cancer activity
3. Amyloid imaging agent in alzheimers disease
4. Anti leishmania activity
5. Anti convulsant activity
6. Anti bacterial and anti fungal activity

7. Cyclogenase inhibitor activity
8. Anti helmenthic activity
9. Anti inflammatory activity
10. Anti malarial activity

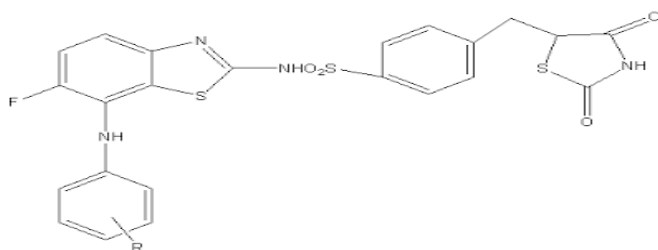
i. Anti tubercular and Anti diabetic activity ^{19,20}:

Some 4-Amino-N-(1,3- benzothiazol-2-yl) benzenesulphonamide derivatives were prepared and found to have good *in-vitro* Antimycobacterial activity (A) against *H37Rv* strain of *mycobacterium tuberculosis* and other derivatives (B) and (C) were also found active as antibacterial and antifungal agents.



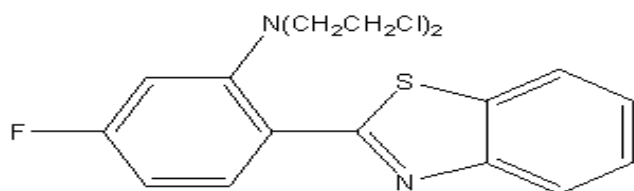
A	Cl	COOH
B	Br	OCH ₃
c	Cl	CH ₃

Synthesized 2-amino [5 (4- sulphonylbenzylidene)-2,4- thiazolidinedione] - 7 - chloro - 6 - fluobenzothiazole series and screened for their antidiabetic activity on albino rat by alloxan induced tail tipping method.

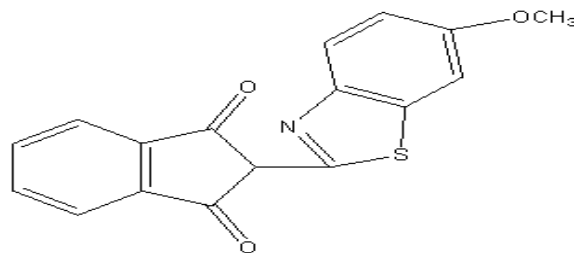


ii. Anti cancer activity: ²¹

Refluxed o-aminophenols with substituted benzoic acid in presence of polyphosphoric acid at higher temperature to get aryl substituted benzothiazoles and evaluated them against Human Cervical Cancer cell lines as anticancer drugs

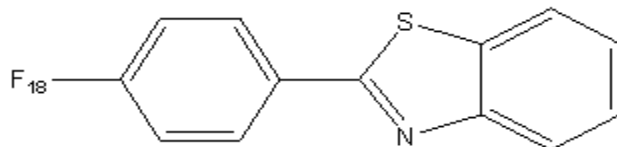


Benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines.



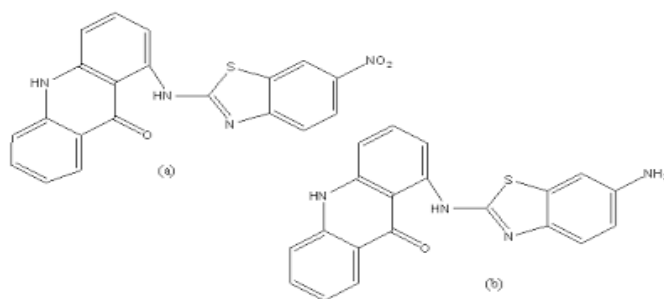
iii. Amyloid imaging agent in Alzheimer's disease ²²

F-labelled 2-(4'-fluorophenyl)-1,3- benzothiazoles. They Evaluated it as amyloidal imaging agent in Alzheimer's disease in comparison with [11C]PIB (11C labelled 6-hydroxy-2-(4''-N- [11C] methyl aminophenol)-1,3-benzothiazole and showed excellent characteristics comparable with those of [11C]PIB, namely good affinity for amyloidal plaques present in human Alzheimer's disease.



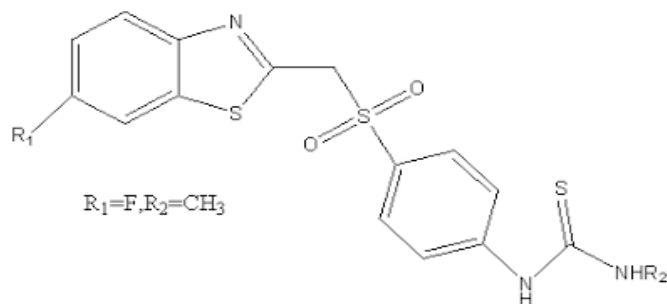
iv. Antileshmanial activity ²³

Acridone derivatives of benzothiazole were synthesized and evaluated for antileshmanial activity towards *Leishmania promastigotes*. Two derivatives, 4- (6- nitro- benzothiazol-2- ylamino)-10H- acridin- 9- one (a) and 1-(6-amino-benzothiazol-2-ylamino)-10- H-acridine-9-one (b) revealed a selective antileishmanial activity. The prersence of a 6-amino benzothiazole group on position 2-amino chain and a 6-nitro benzothiazole group on position 4 amino chain was found essential for antiamastigote properties.



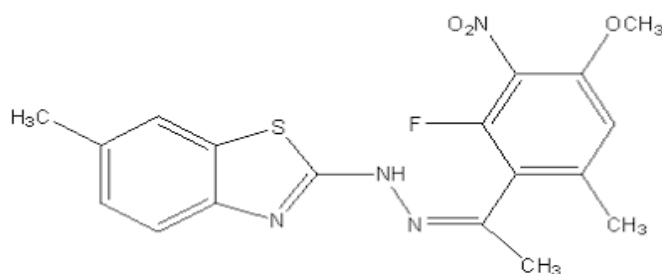
v. Anticonvulsant Activity²⁴

For anticonvulsant activity, a large number of benzothiazole derivatives were evaluated and found to possess significant activity against various types of seizures. In search of potent anticonvulsants containing benzothiazole moiety, a series of N-(6-substituted-1, 3-benzothiazol-2-yl)-4- [(substituted amino) carbonthioyl] amino benzene sulfonamides is active anticonvulsant in MES and PTZ induced seizures



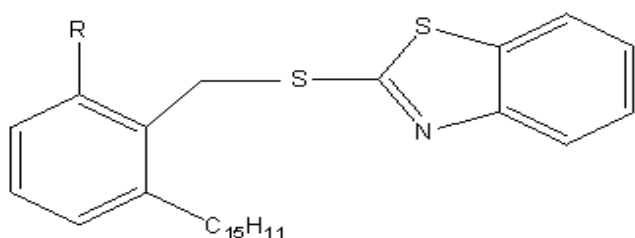
vi. Antibacterial and antifungal activity²⁵

Some 2- substituted benzothiazoles is examined against *E. coli* and *S. aureus* for antibacterial activity and *Candida albicans* and *Aspergillus niger* for antifungal activity. Most of the compounds showed promising results for both activity.



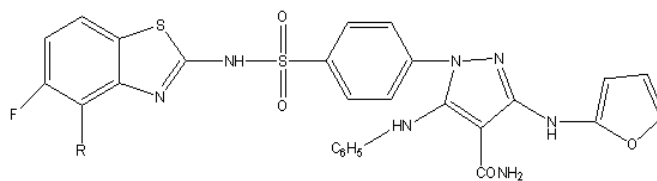
vii. Cyclooxygenase inhibitor activity²⁶

A series of 2-[(2- alkoxy-6-pentadecylphenyl) methyl] thio-1-Hbenzimidazoles/ benzothiazole from anacardic acid (pentadecyl salicylic acid) and investigated their ability to inhibit human cyclooxygenase enzyme-2.



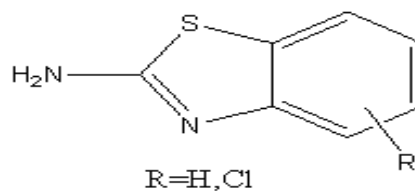
viii. Anthelmintic activity²⁷

Flurobenzothiazole comprising sulfonamide pyrazole derivatives. They screened synthesized for anthelmintic activity by using earthworms (*Peritumaposthum*). Albendazole was used as standard drug. The compounds were evaluated by time taken for complete paralysis and death of worms.



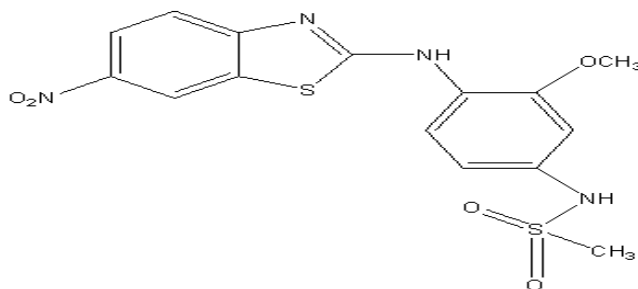
ix. Anti Inflammatory activity²⁸

In the recent years, a large number of benzothiazole based anti-inflammatory agents have been synthesized. Some novel 2-amino benzothiazole derivatives and evaluated them for anti-inflammatory activity. Test compounds showed significant anti-inflammatory activity and it was noted that when the 2-amino benzothiazole is substituted at 4 or 5 positions with electron withdrawing groups like Cl, NO₂, OCH₃ increase in anti-inflammatory activity was found.



x. Antimalarial activity²⁹

Antimalarial activity of 2- substituted-6- nitro and 6-amino benzothiazoles and their anthranilic acids were carried out on W2 and 3D7 strains of *P. falciparum*. The results revealed the potency of compounds as the antimalarial agents of clinical and biological research.



CONCLUSION: Benzothiazole derivatives are an important class of heterocyclic compounds. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. The benzothiazole nucleus containing compounds involved in research aimed at evaluating new products that possess biological activities, such as antimicrobial, antifungal, anthelmintic, anti-diabetic, amyloid imaging agents and anticancer agents.

The versatile synthetic applicability & biological activity of these heterocycle compounds will help the medicinal chemists to plan organize & implement new approaches towards discovery of novel derivatives of benzothiazole.

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