Progress in Chemical and Biochemical Research 2022, 5(2), 147-164

Progress in Chemical and Biochemical Research

Journal homepage: www.pcbiochemres.com

*Review Article*

# A Review on Recent Development and biological applications of benzothiazole derivatives

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**ARTICLE INFO**

**Article history**

Submitted: 2022-01-21
Revised: 2022-02-23
Accepted: 2022-03-27
Available online: 2022-05-08
Manuscript ID: PCBR-2202-1214
**DOI**:
10.22034/pcbr.2022.330703.1214

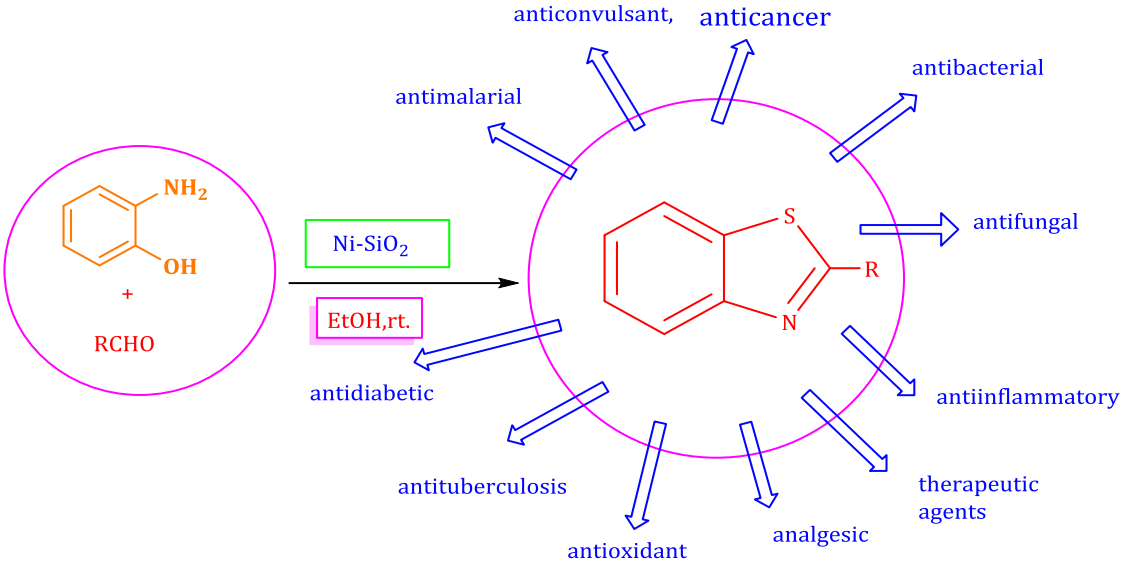
**KEYWORDS**

Benzothiazole
Anti-inflammatory
Anti-convulsant
Anticancer
Antitubercular

**ABSTRACT**

Benzothiazole (BTA) and its derivatives are among the most important heterocyclic compounds, widely found in natural commodities and pharmaceutical drugs. It possesses a large number of pharmacological properties, and many of its analogues have structural diversity, to contribute to the production of new medicinal drugs. BTA derivatives possess a broad spectrum of pharmacological activity. The development of medicinal chemistry containing BTA has been rapid and highly active. BTA chemicals are frequently used in medical care to address a wide variety of illnesses with good results. Current advancements in BTA-based compounds such as anticancer, antibacterial, antifungal, anti-inflammatory, analgesic, antioxidant, anticonvulsant, anti-tuberculosis, antidiabetic, antimalarial, and other therapeutic agents are the focus of this review. New ideas are spurring the development of BTA-containing drugs that are more active, less toxic, and more effective for diagnosing diseases.

**GRAPHICAL ABSTRACT**

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## Introduction

Benzothiazoles are heterocyclic dicyclic compounds consisting of a benzene bonded to amembered ring containing nitrogen and sulfur atoms [1] It possesses a number of biological properties, such as anelgesic [2], antiinflammatory [3], antidiabetic [4] and anticancer [5]. Benzothiazoles are found in anumber of natural substances found in the sea and on land with beneficial biological properties. Benzothiazole is used to treat several diseases, such as neurological diseases, local cerebral ischemia, central muscle relaxants, and cancer [6]. It is easy to obtain the biological properties as a drug carrier for the development of new benzothiazoles. Benzothiazoles are used in many dyes, such as theoflavin [7]. Figure 2 shows a number of commercially available benzothiazole-containing drugs [8-10], some reviews have recently been published in the literature, finding synthetic and biological methods, synthesis techniques, and biological activities of benzothiazoles [11-14].

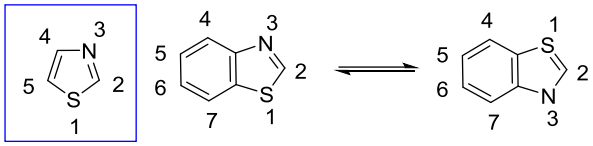


**Fig 1.** Benzothiazole Toutamerism

BTA is a flavor chemical generated by the fungi Aspergillus clavatus and Polyporus frondosus, and is found in tea leaves and cranberries. [15]. They are also used as appetite suppressants [16], dye intermediates [17], plant protectors [18], B-amyloid plaque imaging agents [19], and photographic inducers [20]. BTA derivatives are heterocyclic compounds used in several fields of chemistry, in polymer chemistry [21], dyes [22], pharmaceuticals [23], and in silver photography, BTA salts are used as sensitive dyes [24,25], Benzothiazole is afungicide [26]. Elastomeric unsaturated polymers of BTA derivatives arise from (lattice) sulfide bonds, and the resulting elastic material is crosslinked (MBT/BTSH) is arubber accelerator and is used in a number of specialty products, such as tire manufacturing [27].

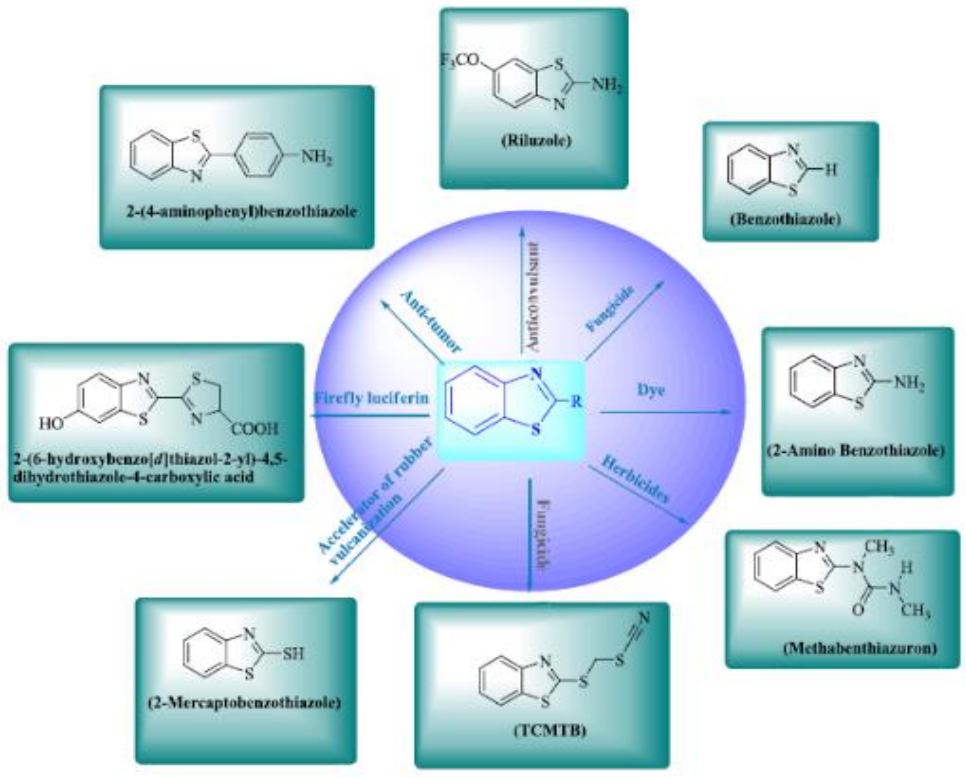
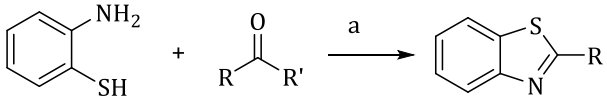



**Figure 2.** Benzothiazole, a multifunctional nucleus.

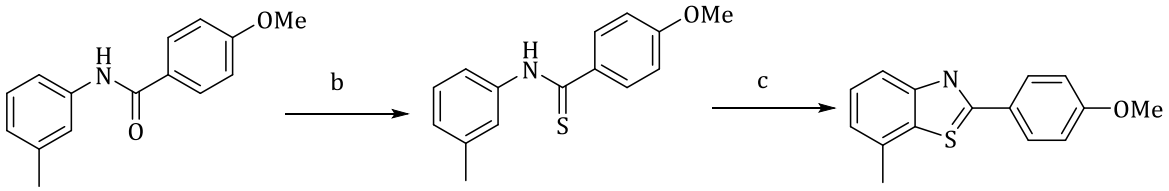
## Chemistry of benzothiazole

Hoffmann first created and published in 1887 a variety of synthetic methods due to the simple mechanics of the splitting [28]. 2-amino thiophenols condensation reaction with nitriles, aldihydes, carbaxylic acids, acylchlorides, oresters to prepared BTA [29]. On the other hand, it is equivalent to such as the rapid oxidation of 2-amino thiophenols with compensators,

Jacobson's prepared BTA from the ring closure of 2-amino thiophenols [30]. Other methods of preparing it from the reaction of 2-amino thiophenols with *p*-chlorocinnamaldehydes using a microwave, and BTA is used in several applications such as the formation of biologically active chemicals and more diverse activity Biology, great interest for the synthesis of BTA derivatives such as Grignard arylsothiocyanate methods [31]. Using several catalysts PCC [32], nanoceria ($CeO_2$) [33], boron trifluoride ethers [34], silica-held copper (II) nanoparticles [35] (Scheme 1).



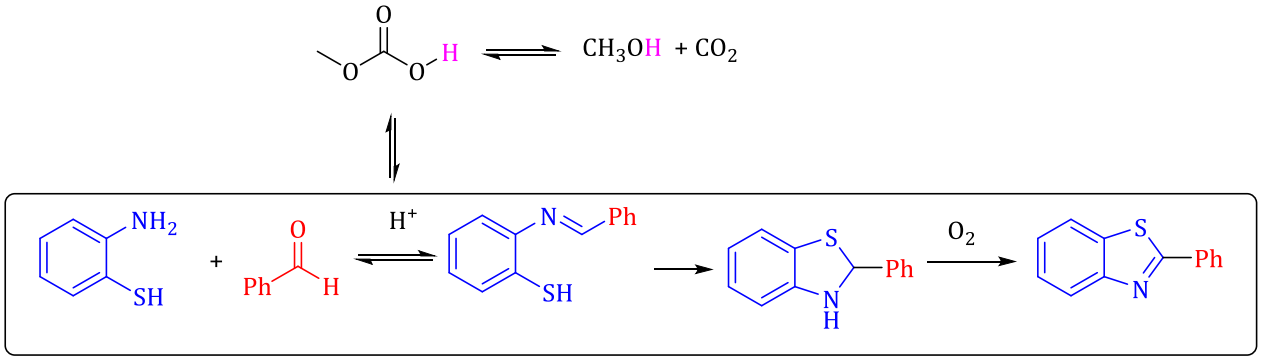

R'= Acid, aldehyde, nitriles, imidates, o-esters, anhydrides, lactons
a = strong acid, milder reagents, oxidative reagent, different catalyst




b= LR, $C_6H_5Cl$, reflux, 65%
c= NaOH, $Fe(CN)_6K_3$

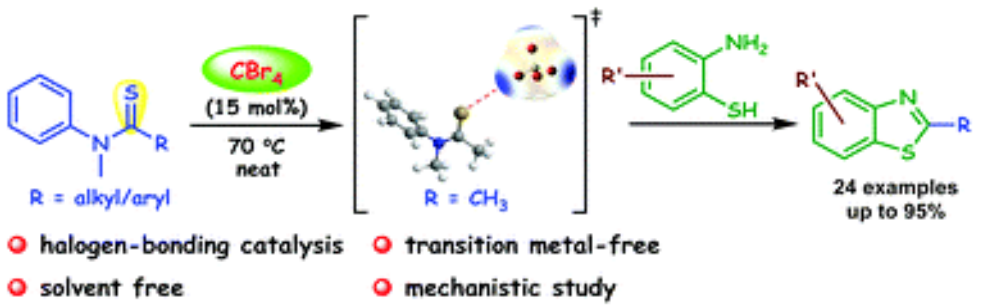
**Scheme 1.** General synthesis of benzothiazole

Xiao Li *et al.* [36] under minor circumstances, a variety of benzothiazole derivatives were produced via reaction and cyclization of 2-aminthiophenol with aliphatic, heteroaryl, and aryl aldehydes, which was aided by alkyl carbonic acid.



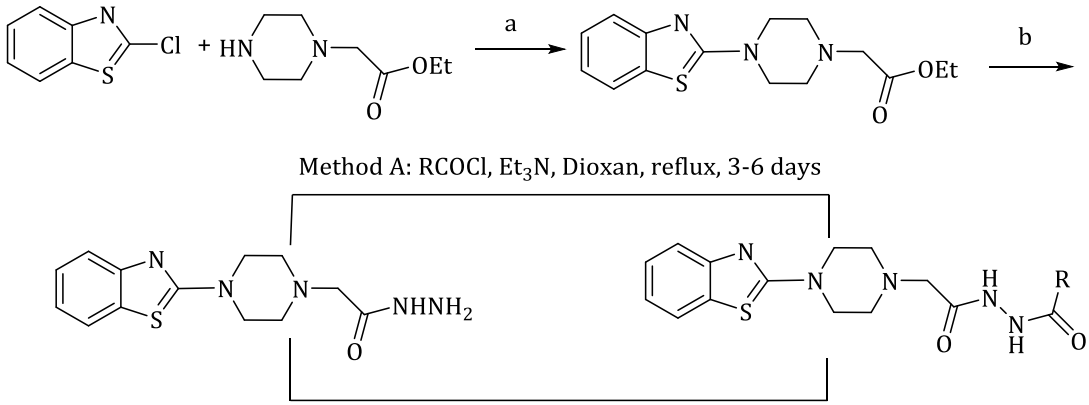

**Scheme 2.** Synthesis of benzothiazole derivatives

Imran Kazi and Govindasamy Sekar, [37] synthesis of 2-substituted benzothiazole from *N*-methyl thioamides and tetrabromomethane by $CBr_4$ as a catalyst, using solvent and metal conditions.



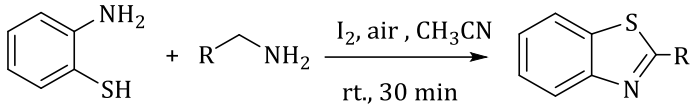

**Scheme 3.** synthesis of benzothiazole derivatives

Mahmoud Al-Talib *et al.* [38] synthesized of new benzothiazol piperazin derivatives form ethyl 2-(4-(benzothiazol-2yl)piparezin-1-yl)acetate and hydrazinehydrate.




**Scheme 4.** synthesis of benzothiazole derivatives (a) EtOH, $NaHCO_3$, ref., 24 h (b) $NH_2NH_2{\cdot}H_2O$, heat

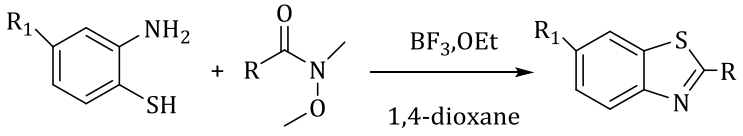
Narender *et al,* [39] synthesized of benzothiazole derivatives using iodine from amine and 2-mercaptoaniline at room temperature.




R= Ph, 4-$OCH_3$-Ph , 4-Cl-ph , 3,4-Cl-Ph , 4-F-ph, 4-$CH_3$-Ph,4-$OCF_3$-Ph

**Scheme 5.** synthesis of benzothiazole

Sadashiva *et al.* [40] synthesized benzothiazoles via condensation and cyclization of amide with oaminothiophenol in $BF_3.OEt_2$ in 1,4-dioxane as a solvent at 100°C, yielding 75–94% in 60 min.

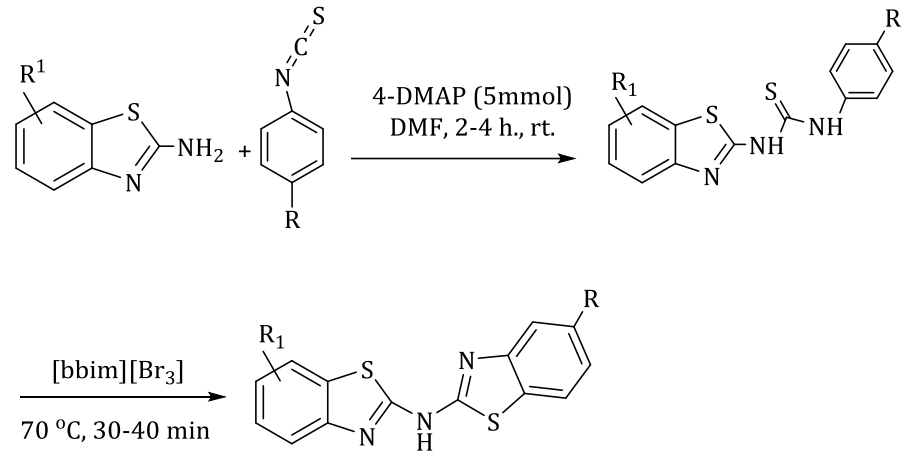



R= Alkyl, Alkenyl, Hetoroaryl

$R_1$ = H, $CH_3$, Br

**Scheme 6.** Synthesis of benzothiazoles

Kumbhare *et al.* [41] Synthesized of benzothiazole by oxidative cyclization of thiourea with [bbim][$Br_3$] ionic liquid under mild conditions from reacting 2-aminobenzothiazole and phenylisothiocyanate in 4-DMAP in DMF at 70 °C.

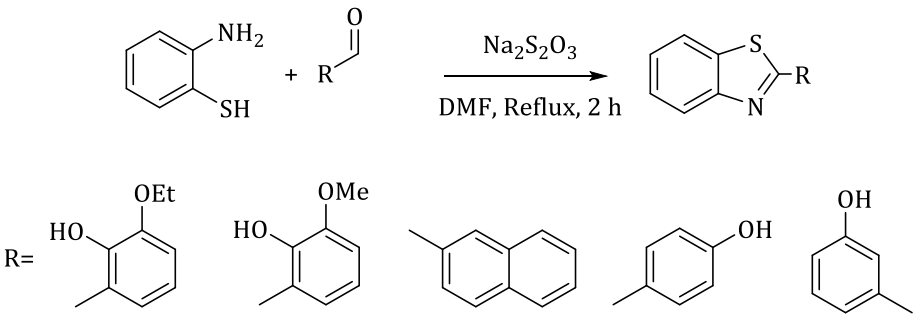



$R^1$=H, 6-F, 6-OMe, 4-Cl

R= H, F, Cl

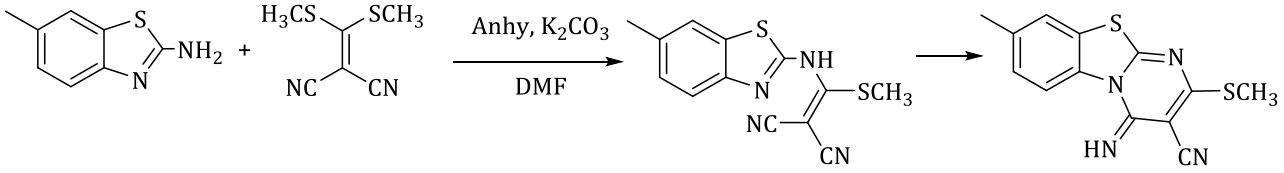
**Scheme 7.** Synthesis of benzthiazole derivatives

Khan *et al.* [42] synthesis of benzothiazole derivatives from 2-aminthiophenol with aromatic aldehydes in (DMF) and ($Na_2S_2O_5$) when there is a reflux 2 h., high yield.




**Scheme 8.** Synthesis of benzothiazoles

Pingle M. S., *et al.* [43] synthesized of 3-cyan-4mino-2methylthio-8methyl4H-pyrimdo[2,1b],[1,3] benzthiazole from 2-amino6-methylbenzthiazole and bis (methylthio)methylne malonitrile .



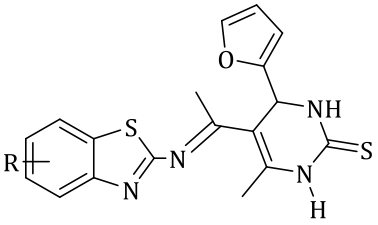

**Scheme 9.** Synthesis of benzothiazole

## Pharmacological actions of BTA

BTA and its analogs are essential pharmacphores and well-known structures in medicinal chemistry, appearing in a variety of clinically useful medicines. As a result, the current review provides a complete summary of current breakthroughs in BTA-based medicinal chemistry, as well as methods and SAR.

### BTA as antimicrobial agents

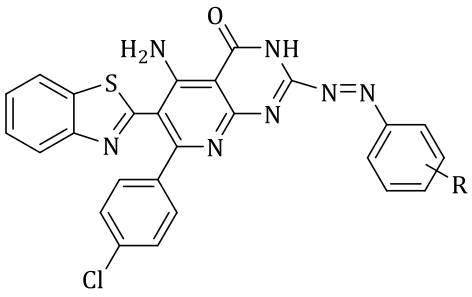
Most of the treatments used as medicines are an antimicrobial agent to prevent the growth and reproduction of bacteria [44]. When used poorly, it leads to the Antibiotic-resistant diseases are becoming more common [45]. Antimicrbial therapy has advanced a lot, Infectious disorders produced by bacteria or fungus, on the other hand, pose a significant threat. Waghamode KT *et al.* [46] produced benzothiazole derivatives and tested antibacterial activity against G+ and G- bacterial. The all compounds have excellent antibacterial activity.



R=H, 4-, 5-, 6- ($NO_2$), 6-, 4- ($CH_3$), 6-$OC_2H_5$

**Figure 3.** Structure of benzothiazole derivatives

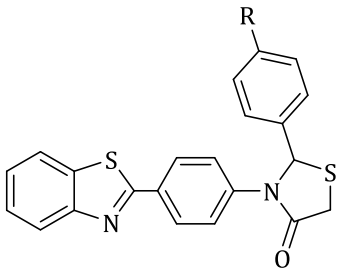
In 2016, Lavanya P *et al.* [47] antibacterial and antifungal activity of benzthiazole pyrimdine derivatives toward Staph. *aureus, E. coli*, *K. pneumoniae*, and Strep.*pyogenes* were examined.



R=H, 5 -$NO_2$, 6-, 4- $(CH_3)_2$, 4-$OCH_3$

**Figure 4.** Structure of benzthiazole pyrimdine derivatives

M. Singh et al, [48] identified series of compounds benzthiazolthiazolidin, hich has the most active antimicrobial action versus E. coli and Candida albicans (MIC1 415.6–125 mg/mL)



R= $CH_3$, OH

**Figure 5.** Structure of benzthiazolthiazolidin

Bele *et al.* [49] synthesized benzthiazole derivatives and *S. aureus, S. pyrogens, E. coli, P. mirabilis* and *A. fumigetus* microorganisms were examined for antibacterial efficacy.

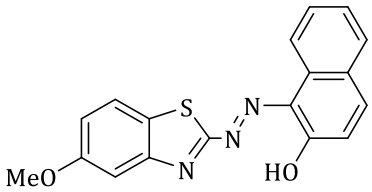
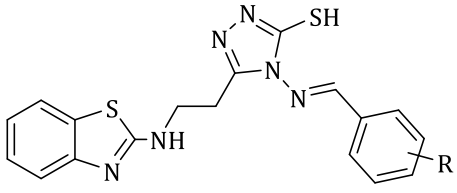


**Figure 6.** Structure of benzthiazole derivatives

Soni and co-workers [50] synthesized a number 5-[2-(1,3benzthiazol-2-ylamino)ethyl]-4-(arylidenemino)-3-mercopt-(4*H*)-1,2,4triazoles, were investigated for antibacterial and antifungal activity



R=$_4$-$N(CH_3)_2$ ,3,4-$OCH_3$

**Figure 7.** Structure of benzthiazole derivatives

H. Al-Tel *et al.* [51] reported imidaz[2,1-b][1,3]benzothiazoles, show high inhibitory

activity against bacterial and fungal compared with(amoxicilin) and antifungal (fluconzole).

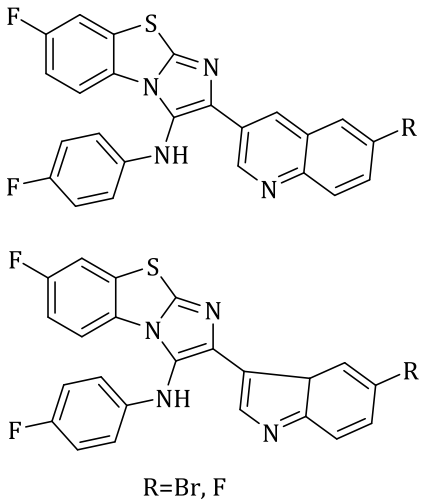



**Figure 8.** Structure of benzthiazole derivatives

P. K. Sahu et al. [52] identified 4-(4-hydroxyphenyl)-4Hpyrmido-[2,1-b]-[1,3] benzthiazole,show antibacterial agent against (*P. aerug., S. typhi, E. coli and P. rettgeri),* compared with slandered ciprofloxacin.

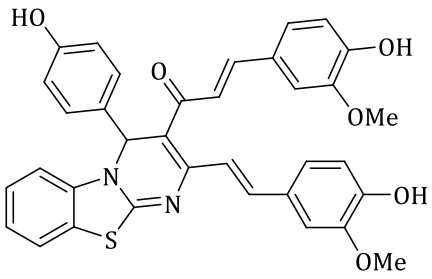



**Figure 9.** Structure of 4-(4-hydroxyphenyl)-4*H*-pyrmido-[2,1-b]-[1,3] benzthiazole

H. R. Tomi H. R. *et al.* [53], study of oxazole and benzothiazole heterocyclic compounds, were detected benzothiazoles in antibacterial assays, most active than oxzole derivatives.

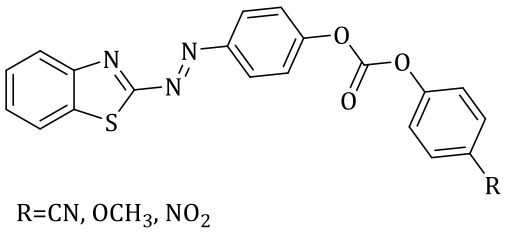



**Figure10.** Structure of benzthiazole derivatives

**BTA as antitubrcular agent**

Tubrculosis (TB) is one of the deadly infectious diseases caused by infection Mycobacterium (tubrculosis, bavis and africonum), and it has a great effect on body tissues, such as the lungs, and antibacterial drugs are ineffective because they generate several metabolic directions and drugs leak through the cell wall. Telvekar *et al.* [62] synthesizednew2-(2(4arylxybenzyldene) hydrzinyl)benzthiazoles from2-hydraznylbenzo-thiazoleand4-(arylxy) benzldehyde, using amolecular hybrdization technique.

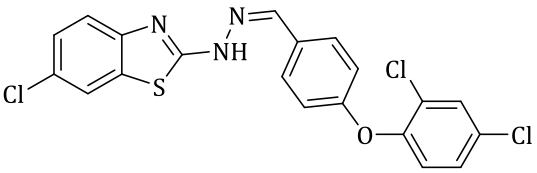



**Figure 11.** Structure of 2-(2-(4arylxybenzyldene) hydrzinyl)benzthiazole

Patel et al. [55] evaluated many derivatives of benzmidazolyl-1,3,4oxadizol-2-ylthio- N-phenyl-(benzothiazolyl)acetamides for anti-M. tuberculosis H37Rv activity .

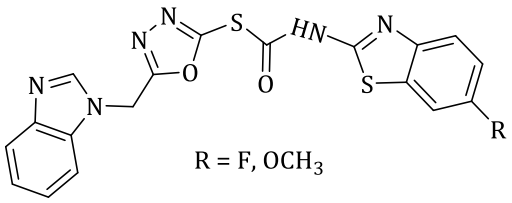
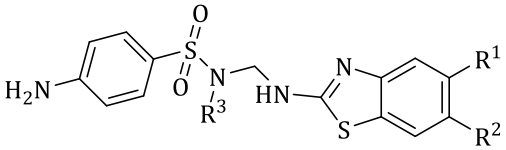



**Figure 12.** Structure of benzthiazole derivatives

N. Nayeem *et al.* [56] synthesized chains of benzthiazole derivatives and the chemicals' potential to fight Mycobacterium




$R^1$ = H, $R^2$ =H, $R^3$=H
$R^1$ = Cl, $R^2$ =H, $R^3$=H
$R^1$ = Cl, $R^2$ =F, $R^3$=H
$R^1$ = Cl, $R^2$ =H, $R^3$=C4H3N2

**Figure 13.** Structure of benzthiazole derivatives

**BTA as Anticancer Activity**

Cancer is a global health problem that kills millions of people and has great difficulties in medicine, to produce powerful new drugs against tumors from global research efforts.

Eman A. Abd El-Meguid *et al.* [57] synthesized of new 2-aryl benzthiazole from 4-oxothiazlidin-2-yldene as well as several amino acids and ester derivatives.

In combination with doxrubicin, the compounds showed cytotxicity toword cancer cell lines (HepG-2 and MCF-7)

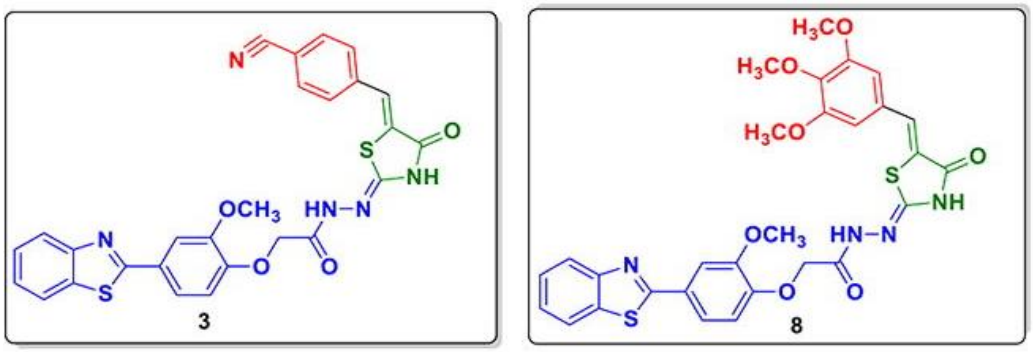



**Figure 14.** Structure of 2-aryl benzthiazole

Suvarna G Kini and colleagues [58] synthesized two aminobenzothiazoles and tested anticancer action. Show *N*-(6-Cl-1, 3benzthiazole-2-yl)-1-(2,5 dimethxyphenyl) methanmine has great action.

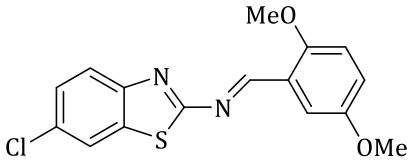



**Figure 15.** Structure of N-(6chlor-1, 3benzthiazole-2-yl)-1-(2,5 dimethxyphenyl) methanmine

Uremic N et al. [59] the chemicals have excellent anticancer activity and were produced benzthiazole derivatives and assessed anticancer activity versus pancreatic cancer cells.

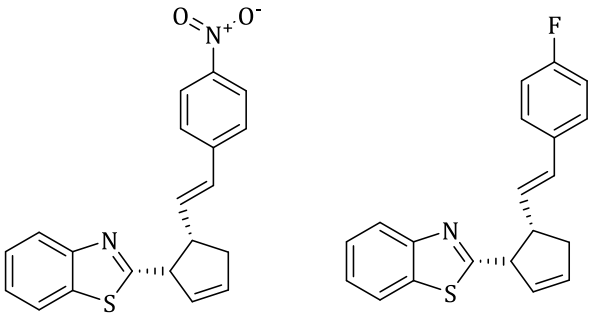



**Figure 16.** Structure of benzthiazole derivatives

Leal K.Z. *et al.* [60] synthesized of 2-benzthiazole hydrzones derivatives. Anticancer activity was also investigated. The anticancer activity of 2-((2-(benzthiazol-2-yl) hydrzono) methyl) benzen1,4-diol has been demonstrated.

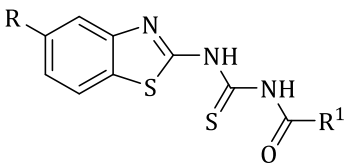
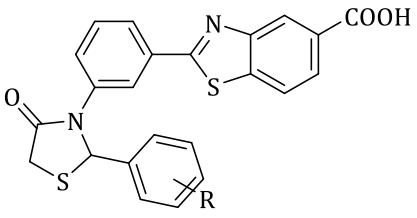



**Figure 17.** Structure of benzthiazole derivatives

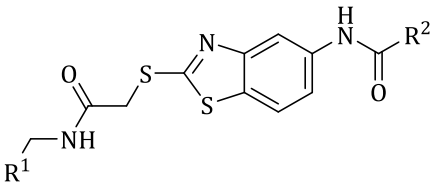
Prabhu *et al.* [61] produced of thiazldinethi-azolecarbxylic acid derivatives from thioglyclic acid using benzothiazole Schifs bases, showed the more important activity.




R=p-Cl, p-$CH_3$,p-OH,p-$OCH_3$

**Figure 18.** Structure of thiazldin ethiazolecarbxylic acid derivatives

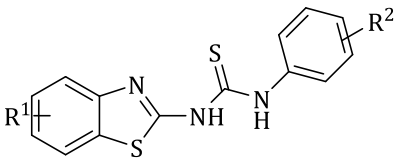
Wang *et al.* [62] New benzothiazolethiol compounds were produced and their antiproliferative properties were tested in HepG2 and MCF-7 cells.



$R^1$ = H, Ph, Ch-Ph
$R^2$ = Me, Ph

**Figure 19**. Structure of benzothiazolethiol

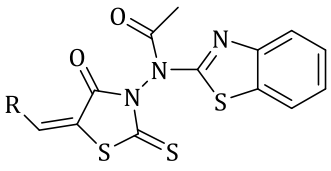
Kumbhare *et al.* [63] synthesized benzothiazolyl-thiocarbamides using acatalytic (DMAP) with [bbim][$Br_3$]. The cytotxic activity of compounds was tested amousemlnoma cell line and two humen moncytic cell lines (U 937, THP-1).



$R^1$ = H, 6-Cl, 6-F
$R^2$ = H, F, Cl

**Figure 20.** Structure of benzothiazolyl thiocarbamides

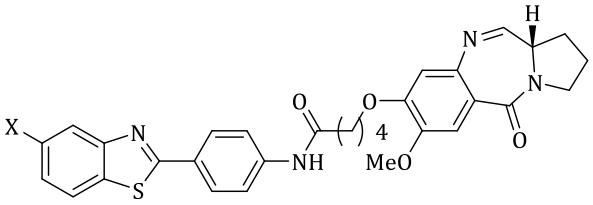
Saeed et al. [64] synthesized of benzothiazol derivatives from new 4-thiazolidinones with benzothiazole. Antimicrobial and anticancer activities are also tested.



R = 4-Cl-Ph, 4-dimethylaminophenyl

**Figure 21.** Structure of benzothiazol derivatives

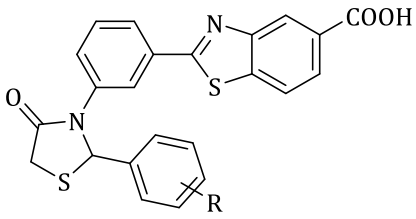
Solomon *et al.* [65] asequence of pyrrolbenzo-diazepine with benzthiazole and examined the antibreast cancer effect cell lines, MDAMB231, MDA-MB468, and MCF7.



X = H, F

**Figure 22.** Structure of benzothiazol pyrrol benzodiazepine derivatives

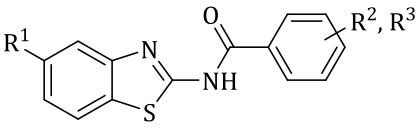
Kamal *et al.* [66] created 2-(3-(4-oxo2-substtuted phenylthiazlidin- 3-yl)benz[d]thizole-6-carboxyl-icacid derivatives. Anticancer activity was studied in ahumen melanma cell line (A375).



R = H, 4-Cl, 3-F, 4-$NO_2$, 3-$OCH_3$

**Figure 23.** Structure of benzothiazol derivatives

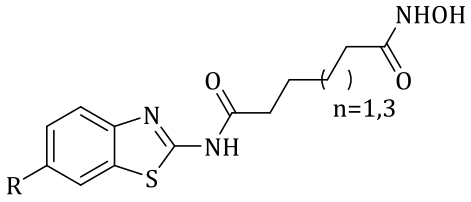
Caputo *et al.* [67] synthesized of benzothiazole derivatives with anarylamide or an arylurea 60 human tumor cell lines were investigated in apreliminary anticancer assay.



$R^1$= OMe, $OCF_3$
$R^2$ = 4-F, 2-F, 4-OMe
$R^3$ = H, 6-F

**Figure 24.** Structure of benzothiazol derivatives

Oanh *et al.* [68] produced benzothiazole contain analogues of SAHA andtarget Histone deacetylase (HDAC) enzymes of classes I and II.




R= H, $CH_3$, OMe, OEt

**Figure 25.** Structure of benzothiazol derivatives

**BTA as Antimalarial drug benzothiazoles**

Malaria is one of the parasitic diseases transmitted bitten by an infected Anopheles mosquito everywhere in the globe. To avoid it, it is preferable to use antimalarial drugs in a preventive manner and to be in several groups, and some of these drugs are good and resistant to mosquitoes [69].

Sarkar S et al. [70] synthesized and tested benzothiazole derivatives for antimalarial activity found 4-(2-(benzthiazl-2-yl)hydrazon)metthyl) benzen-1, 2-diol has the more action.

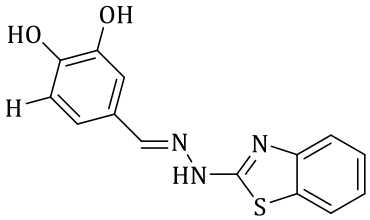



**Figure 26.** Structure of benzothiazol derivatives

Ongarora *et al.* [71] developed of amodiaquine correspondents of benzothiazoles Plasmdium falciprum W2 and K1 chlorquinresistant isolates were used to assess antiplasmodial activity.

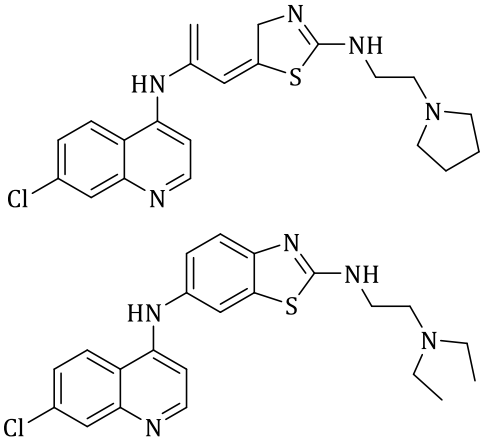
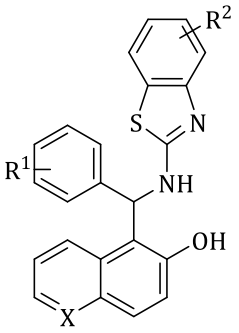



**Figure 27.** Structure of modiaquine benzothiazol derivatives

Venugopala *et al.* [72] several benzthiazole derivatives were also studied for their mosquito repellent effects against Anophles crossed.




X=CH,N

$R^1$=4-OH, $NO_2$, H, $OCH_3$

$R^2$= 6-Cl, 6-Br, 4-$CH_3$

**Figure 28.** Structure of benzothiazol derivatives

**BTA as anti-inflammatory**

Manu Kumar *et al.* [73] synthesized benzothiazole berberine derivatives and shown the cytopethic effect (CPE) and sulforhdamine B (SRB) assays, the activity against some influenza virus was determined. In 2015, Sadhasivam G et al. [74] created and evaluated benzothiazole for anti-inflammatory action. It was shown that N-(6-[(4-cyclhexylphenyl)sulfnyl] amino-1, 3-benz thiazl-2-yl) cetamide has more action.

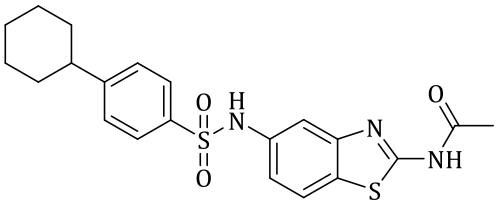



**Figure 29.** Structure of *N*-(6-[(4-cyclhexyl phenyl)sulfnyl] amino-1, 3benz thiazl-2-yl) cetamide

In 2013, Kashinath DV *et al.* [75] produced and evaluated pyrimid [2, 1-b] [1, 3] benzthiazole derivatives and show fairly active for antiinflammatory action.

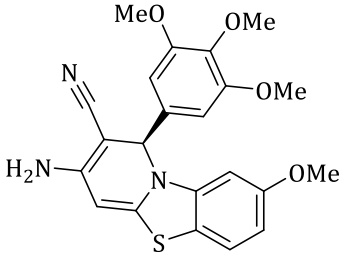
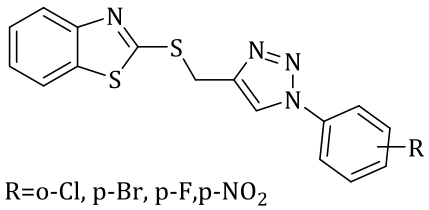


**Figure 30.** Structure of pyrimid [2, 1-b] [1, 3] benzthiazole

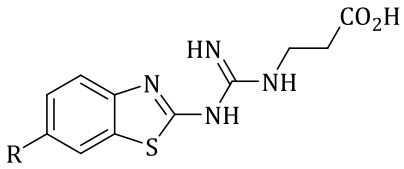
In 2014, Shafi *et al.* [76] synthesized 2-mercaptbenzothiazole andtriazole derivatives (COX) activity tests and caragenaninduced were used to evaluate antiinflammatory effect of the compound



R=o-Cl, p-Br, p-F,p-$NO_2$

**Figure 31.** Structure of 2-mercaptbenzothiazole riazole derivatives

Venkatesh P *et al.* [77] prepared 1,3-benzthiazole-2-mines of three compounds, (5-chloro-1, 3-benzthiazole-2-mine), 12b (6-methaxy-1, 3-benzthiazole-2-mine), and (4-methoxy1, 3-benzthiazole-2-mine), were show more anti-inflammatory active.



R=$_4$-Cl,5-$OCH_3$,6-$OCH_3$

**Figure 32.** Structure of 1,3-benzthiazole-2-mines

Gurupadayya *et al.* [78] synthesized benzthiazole derivatives azatidin-2ones and thiazline-4ones and investigated them for antiinflammatory activity. Used diclofnac sodium as acommon medicine.

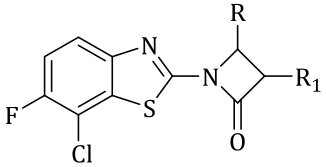


**Figure 33.** Structure of benzthiazole derivatives

Parmshivappa R *et al.* [79] synthesized of 2-[(2alkoxy6-pentdcylphenyl) methylthio-1*H*-benz-imdzoles/benzthiazles from (pentadecyl salicy-licacid) and tested to inhibit human cycloxygenase enzyme230.

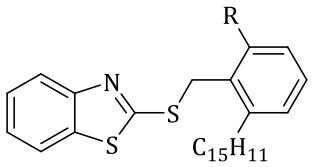


**Figure 34.** Structure of benzthiazole derivatives

**BTA as Anticonvulsant Activity**

Raju GN *et al.* [80] synthesized benzothiazole derivative and found below compounds, have good anticonvulsant Activity.

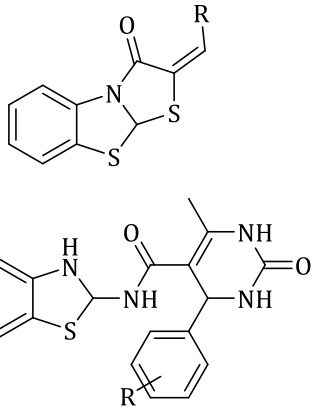


**Figure 35.** Structure of benzthiazole derivatives

Jin *et al.* [81] synthesized benzthiazole derivatives and discovered Anticonvulsant properties of 2-((1H-triazolyl)thio)-*N*(3-fluorbe-nzyl)oxy) benzthiazol-2-yl) acetamide.

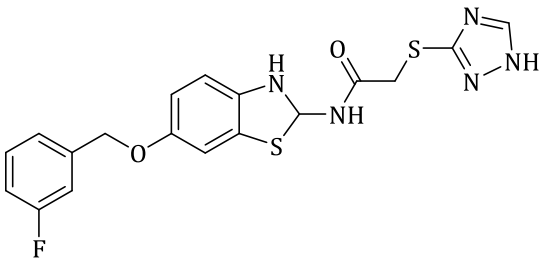
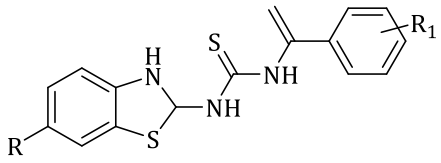


**Figure36.** Structure of benzthiazole derivatives

Amnerkar N *et al.* [82] produced a series of N-substtuted-2-yl)-4-[(substitutedamino) carbnothioyl] aminbenzene sulfonmides from prop-enemido, and 1acetyl-pyrazline derivatives and have high anticanvulsant action.



R = Br, Cl, F, $NO_2$, $CH_3$, $OCH_3$
$R_1$ = H, 2-Cl, 4-cL, 4-$OCH_3$

**Figure 37.** Structure of benzthiazole derivatives

**BTA as antioxidant**

Ahmed El-Mekabaty *et al.* [83] produced a series of benzothiazole derivatives and found antioxidant action and cytotoxicity against the colon cancer cell line (HCT116).

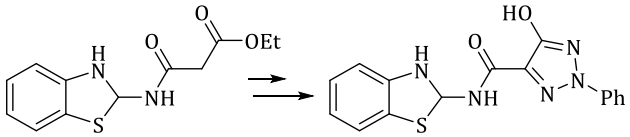


**Figure 38.** Structure of benzthiazole derivatives

Amin S *et al.* [84] produced benzothiazole derivative and show 4-benzthiazole ethoxyphenol .Antioxidant activity is high.

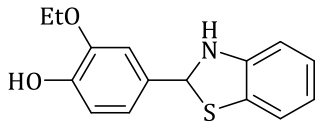


**Figure 39:** Structure of benzthiazole derivatives

Starcevic K et al. [85] synthesized amidinbenzthiazole derivetives and found 6-Amidnium2-(2, 3, 4-trihydrxyphenyl) benzthiazole chloride have goodantioxidant action.

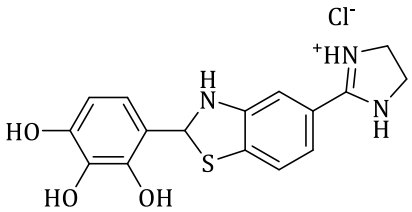


**Figure 40**. Structure of amidinbenzthiazole derivatives

Rosales-Hernandez MC *et al.* [86] synthesized benzthiazole derivatives, found ((benzthiazolylimin(methyl) methylmino)-2-hydroxybenzoicacid having a higher level of antioxidant activity.

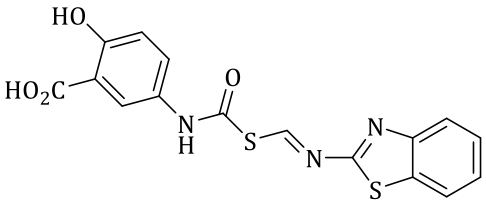


**Figure 41.** Structure of benzthiazole derivatives

Guzel et al. [87] synthesized group of 3HSpir [benzothiazole-indol]-20(10*H*)ones and found has more scavenging activities against DPPH and(ABTS+)radicals.

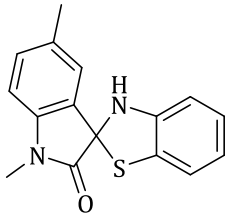


**Figure 42.** Structure of 3*H*-Spir[benzothiazole-indol]-20(10*H*)ones

Cressier D *et al.* [88] synthesized benzothiazoles and thiadiazolderived compounds found 1,5-dimethyl-3H-spir[benz[d]thiazl2,3-indolin]-2-one has a high antioxidant activity.

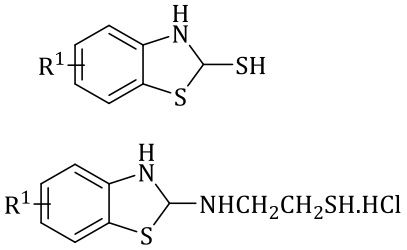


**Figure 43.** Structure of benzothiazoles derivatives

**BTA as antidiabetic Activity**

Kumar et al. [89] produced 2-((benzthiazole-2ylthio) methyl)-5- and found that they have more antidiabetic efficacy.

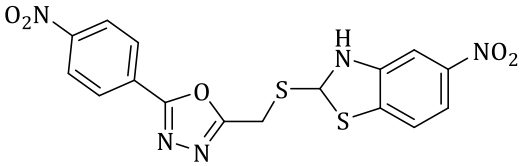


**Figure 44.** Structure of 2-((benzthiazole-2ylthio) methyl)-5benzthiazole

In 2013, Sasson S *et al.* [90] produced benzothiazole derivatives and tested antidiabetic ability, show 2- (benz[d] thiazol-2ylmethylthio)-6-ethoxybenz[d]thiazole has moral antidiabetic activity.

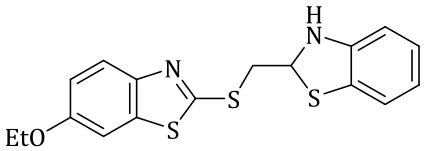


**Figure 45.** Structure of benzothiazole derivatives

Mariappan G *et al*. [91] synthesized abenzo-thiazole derivative and show the N-(6-chlorben-zoat[d] thiazol2-yl)-2-morpholinocetamide has antidiabetic action.

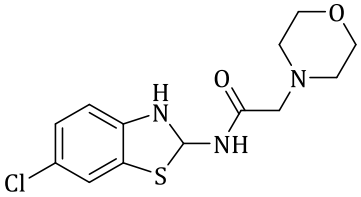


**Figure 46.** Structure of abenzothiazole derivative

## Conclusion

Through the review, we conclude that benzothiazoles are molecules that have several uses and functions with a therapeutic ability in a group of diseases such as cancer, diabetes and others, a diuretic drug (Ethoxolamide), an anti-Parkinson's disease drug (Pramipexole), and a treatment for Alzheimer's disease (Thioflavine)., the production of a good drug by conducting a lot of research, and this indicates the existence of successful conditions for the medicinal substance.

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**HOW TO CITE THIS ARTICLE**

Hala Shkyair Lihumis, Ameer A.Alameri, Rawaa Hefdhi zaooli, A Review on Recent Development and biological applications of benzothiazole derivatives, Prog. Chem. Biochem. Res, 5(1) (2022) 147-164.

**DOI:** 10.22034/pcbr.2022.330703.1214

**URL:** http://www.pcbiochemres.com/article_149460.html