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BENZOTHIAZOLE DERIVATIVE: A REVIEW ON ITS PHARMACOLOGICAL IMPORTANCE TOWARDS SYNTHESIS OF LEAD

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Keywords:

Microsomal triglyceride transfer protein (MTP) inhibitors, Antimicrobial, Anthelmintic, Anticancer, Antioxidant

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ABSTRACT: Heterocyclic chemistry plays a very most important role in medicinal chemistry as well as in organic chemistry. Most of the drug molecule formed and possesses therapeutic activity due to the heterocyclic scaffold. A slight change in heterocyclic moiety leads to the major therapeutic change in the drug molecule. Benzothiazole can serve as a unique and versatile moiety for experimental drug design. Benzothiazole and its derivatives are the essential chemical compounds with tremendous application in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. As we know that benzothiazole is a combination of two rings six-membered and five-membered and it is also known that both rings are responsible for the therapeutic activity. The main objective of our study is to find what changes lead to a better corrective benzothiazole shift moiety. A well-known approach to design new drug-like molecules, which allows achieving new pharmacological profile, action, toxicity lowering, is the development of a combination of 2- aminobenzothiazoles with another heterocyclic ring. A literature search was conducted on the databases namely Science direct, and PubMed with the help of the combination of different keywords: "Benzothiazole," "antimicrobial activity, anticancer, anti-diabetic, anthelmintic activity." The search was customized by applying the appropriate filters to get the most relevant articles to meet the objective of this review article. There is a various number of research and review article present of benzothiazole derivative in case of different disease which concluded that the benzothiazole is one of the most important scaffolds for the treatment of various disease.

INTRODUCTION: Hantzsch and Waber first described Thiazolein 1887 and its structure confirmed by Popp in 1889. In thiazole, moiety numbering starts from the sulfur atom. The basic structure of benzothiazole is the combination of a benzene ring fused with 4, 5 positions of thiazole.

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Thiazole is a heterocyclic compound. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring. Thiazole and their analogs such as benzothiazole play an essential role as a template in the development of tremendous derivatives of thiazole which have different pharmacological activity and useful in the treatment of various disease [1].

Benzothiazole is the combination of two rings, which contain the heterocycles thiazole and benzene. The core structure of thiazole and its pharmacologically and biologically active compounds are due to the presence of sulfur and

nitrogen atoms present in the ring [2]. Various marine or terrestrial natural compounds, which have useful biological activities is due to the presence of the benzothiazole ring [3]. Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2 ºC and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25 ºC). Benzothiazole has no household use. It is used in industry and research work purpose which are very beneficial for the development of the various pharmaceutical compound [4].

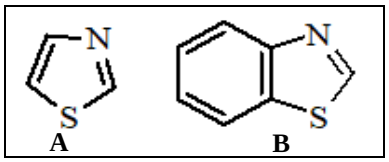


FIG. 1: STRUCTURE OF A) THIAZOLE AND B) BENZOTHIAZOLE

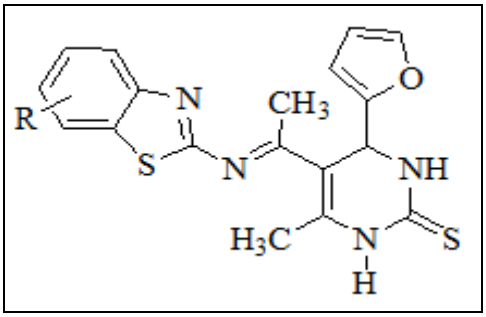
Benzothiazole is one of the most important heterocyclic compound, a weak base, having varied biological activities and still of great scientific interest nowadays. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole is a privileged bicyclic ring 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 [5].

Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial [6, 7, 8, 9, 10] anticancer [3, 11, 12, 13, 14] anthelmintic [15], and anti-diabetic [16] activities. They have also found application in industry as antioxidants, vulcanization accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to the unique structure and its uses as radioactive amyloid imagining agents [17] and anticancer agents [18]. In this review, we have discussed in brief about some commonly developed benzothiazole derivatives and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses.

MATERIAL AND METHODS: A literature search was conducted on various database sources (like PubMed, ScienceDirect) with the help of a combination of different keywords: Benzothiazole, thiazole, antitumor, anti-inflammatory activity, anti-convulsant, antioxidant, anti-mutagenic, anti-diabetic, anti-hyperplasia, and antimicrobial. The search was customized by applying the appropriate filter to get the most relevant articles to meet the objective of this review.

Therapeutic Potential of Benzothiazole:

Anti-Microbial Activity: In 2017 Waghamode KT *et al.*, synthesized some benzothiazole **Fig. 2** derivatives and evaluated their antibacterial activity against gram positive and gram negative bacterial culture and in their study, they found that all synthesized compound posses good antibacterial activity [19].



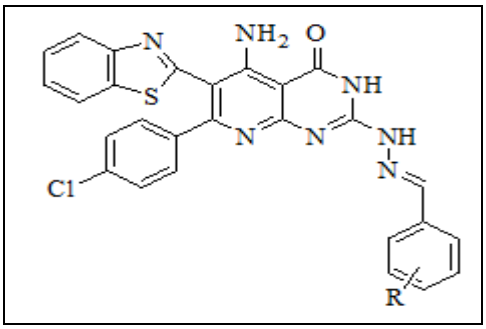
1	H	6	4,6,7- Tri Cl
2	$6OC_2H_5$	7	5- CH_3
3	5-NO_2	8	4- NO_2
4	6 CH_3	9	6- NO_2
5	4 Cl	10	5,6-di- CH_3

FIG. 2: WAGHAMODE KT *et al.*, SYNTHESIZED BENZOTHIAZOLE DERIVATIVE

In 2013 Lavanya P *et al.* synthesized some benzothiazole pyrimidine derivatives **Fig. 3** and evaluated their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* and antifungal activity evaluated against *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, *Penicillium marneffei*, and *Mucor* and in their study, they found that the following compound possesses excellent activity [20].

In 2012 Bele DS *et al.*, synthesized benzothiazole derivative **Fig. 4** and evaluated their antimicrobial activity against *S. aureus, S. pyrogens, E. coli, P. mirabilis, C. albicans,* and *A. fumigatus* microbes and compared with Ciprofloxacin and Amphotericin B which are taken as a reference.

In their study, they found that compound 1-[2-(6-methoxy benzothiazole-2-yl diazenyl]) naphthalene-2-ol, possess good antimicrobial activity [21].



S. no.		Compound name
1	$4CH_3O$	5-Amino-6-(benzo[d]thiazol-2-yi)-2(2-(4-methoxybenzylidene) hydrazinyl-7-(4-chlorophenyl) pyrido [2,3-d] pyrmidin-4(3H)-one
2	4-F	5-Amino-6-(benzo[d]thiazol-2-yi)-2(2-(4-fluorobenzylidene) hydrazinyl-7-(4-chlorophenyl) pyrido [2,3-d] pyrmidin-4(3H)-one
3	$5\text{-}NO_2$	5-Amino-6-(benzo[d]thiazol-2-yi)-2(2-(4-nitrobenzylidene) hydrazinyl-7-(4-chlorophenyl) pyrido [2,3-d] pyrmidin-4(3H)-one
4	$2,4\text{-}(CH3)_2$	5-Amino-6-(benzo[d]thiazol-2-yi)-2(2-(4-dimethylbenzylidene) hydrazinyl-7-(4-chlorophenyl) pyrido [2,3-d] pyrmidin-4(3H)-one
5	$4\text{-}C_2H_5$	5-Amino-6-(benzo[d]thiazol-2-yi)-2(2-(4-ethylbenzylidene) hydrazinyl-7-(4-chlorophenyl) pyrido [2,3-d] pyrmidin-4(3H)-one

FIG. 3: LAVANYA P *et al.*, SYNTHESIZED BENZO-THIAZOLE PYRIMIDINE DERIVATIVES

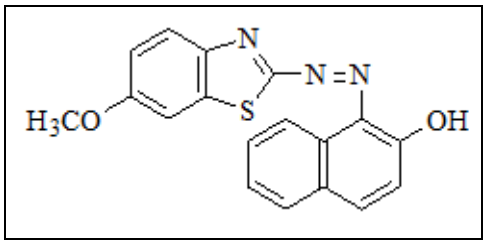


FIG. 4: STRUCTURE 1-[2-(6-methoxy benzothiazole-2-yl diazenyl]) naphthalene-ol

In 2011 Sekar N *et al.*, synthesized some 2 substituted benzothiazole derivative. **Fig. 5** and evaluated their antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Candida albicans* and *Aspergillus niger* by using serial dilution method. In their study, they found that compound 2-(1, 3-Benzothiazole-2-yl)-5-(N, N-diethylamino) phenol possesses good antifungal property [22].

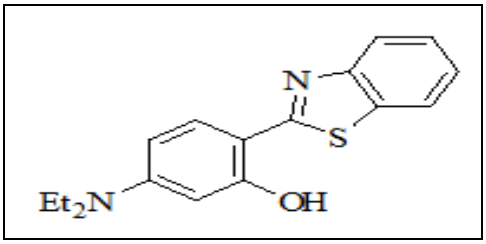
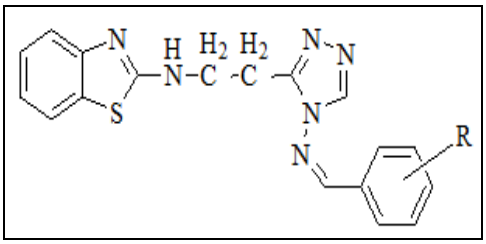


FIG. 5: 2-(1,3-benzothiazole-2-yl)5-(n,n-diethylamino) phenol

In 2010 Soni *et al.*, synthesized a novel series of Schiff bases18 of benzothiazole derivatives and screened them for their *in-vitro* antimicrobial activity against bacterial strains *B. subtilis, E. coli*, *S. griseus*, and *C. albicans, A. niger*. Among synthesized benzothiazole derivatives, compound 1a and 1b having fungal strains substitution showed in **Fig. 6** found to possess maximum activity against both the *C. albicans* and *A. niger* [23].



R= 4- N(CH_3) **R= 3,4-OCH_3**

FIG. 6: SCHIFF BASES OF BENZOTHIAZOLE DERIVATIVES

In 2009 Geronikaki *et al.* prepared a series of N-(benzo[d] thiazol-2-yl)-4 -nitrobenzene sulfonamides for their antimicrobial activity19 against a panel of selected gram-positive and gram-negative bacteria, yeasts, and mold. Among synthesized compounds, the compound showed in **Fig. 7** was found to have possessed maximum activity against Gram-positive and Gram-negative bacteria [24].

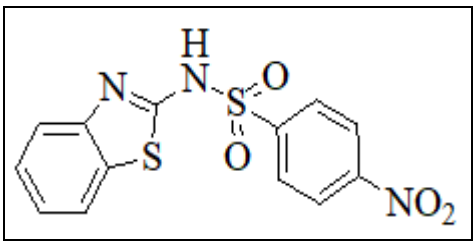


FIG. 7: STRUCTURE of N-(benzo[d]thiazol-2-yl)-4-nitro benzenesulfonamide

In 2010 Jagtap *et al.*, prepared N-(6-fluoro-7-(piperazine-2-yl) benzo [d] thiazol-2-yl)-4-(2-(3-nitrophenyl)-4 -oxothiazolidin-3 -yl) benzene sulfonamide **Fig. 8** and screened for anti-microbial activity [25].

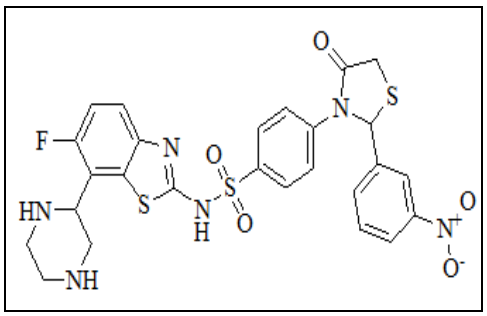


FIG. 8: STRUCTURE OF N-(6-fluoro-7-(piperazine-2-yl) benzo [d] thiazol-2-yl)-4-(2-(3-nitrophenyl)-4-oxothia-zolidin-3-yl) benzenesulfonamide

In 2009 Amir M *et al.*, synthesized 1, 3, 4-thiadiazole and imidazoline derivatives **Fig. 9** containing benzothiazole and screened for both antibacterial and antifungal activity uses cup-plate agar diffusion method. Ofloxacin (50 µg/ml) and Ketoconazole (50 µg/ml) were used as std. drug for antibacterial and antifungal activity respectively. The antimicrobial screening was performed against *E. coli, S. aureus, C. albicans* and antifungal activity against *Aspergillus flavus* and *Candida albicans* [26].

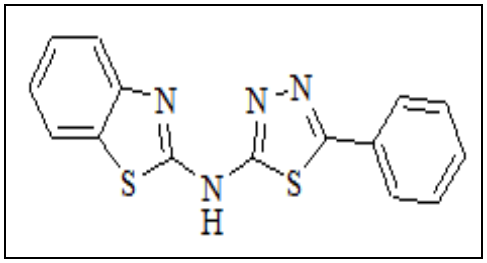


FIG. 9: STRUCTURE OF N-(5-phenyl-1,3,4-thiadiazol-2-yl) benzo [d] thiazol-2-amine

In 2008 Murthi *et al.*, prepared some new 2-mercaptobenzothiazoles 22 and correlated the effect on antimicrobial potency by varying the substituents in benzene part of the benzothiazole ring system. Among synthesized compound **Fig. 10** was most active for antimicrobial activity against *E. coli, S. aureus, C. albicans* and antifungal activity against *Aspergillus flavus* and *Candida albicans* [27].

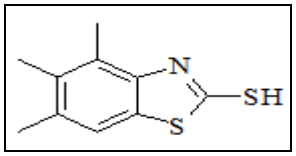


FIG. 10: STRUCTURE OF 4, 5, 6-trimethyl benzo [d] thiazole-2-thiol

Anti-Cancer Activity: In 2018 Ozkay Y *et al.*, synthesized new benzothiazole acylhydrazones derivatives **Fig. 11** and evaluated its anticancer activity. In their study, they found that compound 2-((5-Chlorobenzothiazol-2-yl) thio)-N-(4-(3 methyl piperidine-1-yl) benzylidene) acetohydrazide possess good anticancer activity [28]. In another study, Suvarna G Kini *et al.*, synthesized 2 amino benzothiazole and evaluated their anticancer activity. In their study, they found that compound (E)-N-(6-chloro-1, 3-benzothiazole-2-yl)-1-(2, 5 dimethoxyphenyl) methanimine, possess excellent activity [29].

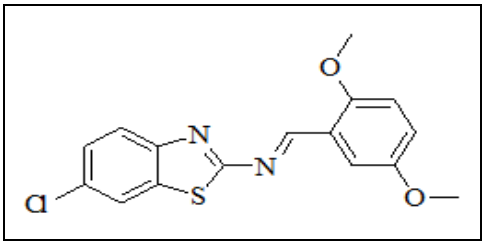


FIG. 11: STRUCTURE OF (E)-N-(6-chloro-1,3-benzo-thiazol-2-yl)-1-(2,5 dimethoxyphenyl) methenamine

In 2017 Uremic N *et al.*, synthesized 2 substituted benzothiazole derivatives **Fig. 12** and evaluated their anticancer activity against pancreatic cancer cell and in their study, they found that compound (a) (b) possess good anticancer activity [30].

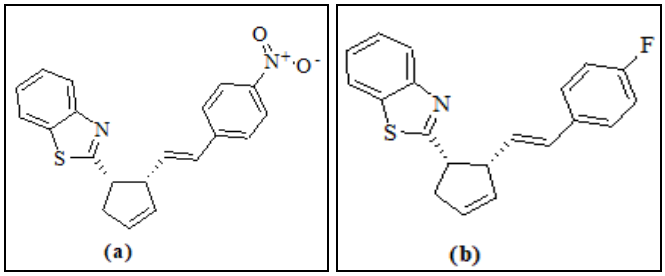
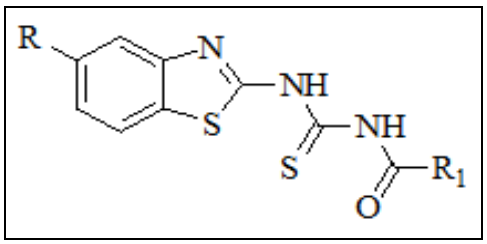


FIG. 12: STRUCTURE OF (a) 2-((1S, 2S)2-((E)-4-nitrostyryl) cyclopent-3-en-1-yl) benzo [d] thiazole (b) 2-((1S, 2S)2-((E)-4-florostyryl)cyclopent-3-en-1-yl) benzo [d] thiazole

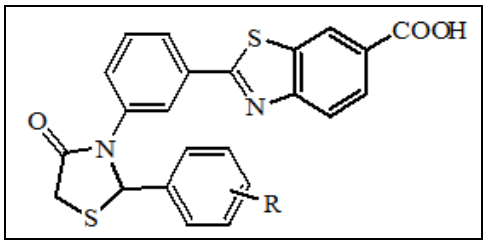
In 2016 Leal KZ *et al*, synthesized different derivatives **Fig. 13** or (E)-2-benzothiazole hydrazones compound and evaluated their anticancer activity. In their study, they found that the compound (E)-2-((2-(benzo[d]thiazol-2-yl) hydrazono) methyl) benzene- 1,4-diol possess good anticancer activity [31]. In 2010 Saeed *et al*, prepared five series of thiourea derivatives bearing benzothiazole moiety and evaluated for their anticancer activity. In preliminary MTT [3-(4, 5-dimethyl thiazol-2-yl) -2, 5- diphenyltetrazolium bromide] cytotoxicity studies, the thiourea derivatives a, b and c having substitution shown in were found most potent [32].



	R	R_1
a	Br	2-thiophene
b	NH_2	4-morpholine
c	Br	4-morpholine

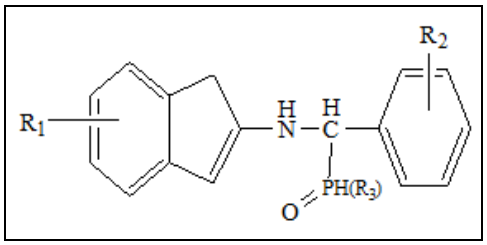
FIG. 13: STRUCTURE OF THIOUREA DERIVATIVES BEARINGS BENZOTHIAZOLE MOIETY

In 2012 prabhu *et al.*, synthesized a series of 2-(3-(4-oxo-2-substituted phenyl thiazolidine-3- yl) phenyl) benzo [d] thiazole-6-carboxylic acid derivatives **Fig. 14** which were synthesized by various benzothiazole Schiff's bases by reaction with thioglycolic acid. Among this compound, 7a exhibited the most significant activity as compared with b, c, and d [33].



a	p-Cl
b	p-OCH_3
c	p-CH_3
d	p-OH

FIG. 14: STRUCTURE OF 2-(3-(4-oxo-2-substituted phenyl thiazolidine-3-yl) phenyl) benzo [d] thiazole-6-carboxylic acid DERIVATIVES



R_1	R_2	R_3
4-CH_3	2-F	n-Bu

FIG. 15: STRUCTURE OF N-(dihydro phosphoryl (phenyl) methyl)-1H-inden-2-amine DERIVATIVES

In 2006 Song *et al.*, synthesized a series of a-Aminophosphonates containing benzothiazole and fluorine moiety; (8 a-m) were synthesized by Mannich-type addition in ionic liquid media with high yield and short reaction time. The newly synthesized compounds were evaluated for their anticancer activities against PC3, A431, A375, and Bcap37 cells *in-vitro* by the MTT method. Compound 8c is highly effective against PC3 cells and moderate to A431 cells [34]. In 2007 Kini S *et al.*, refluxed o-aminophenol with substituted benzoic acid in the presence of polyphosphoric acid at a higher temperature to get aryl substituted benzothiazoles **Fig. 16** and evaluated them against Human Cervical Cancer cell lines as anticancer drugs [12]. In 2010 Devmurari *et al.*, prepared a series of seven substituted 2-phenyl benzothiazoles **Fig. 17** and substituted 1, 3-benzothiazole-2-yl-4-carbothioate derivatives. All synthesized novel compounds were screened for anticancer activity and compounds (a) and (b) showed very good anticancer activity [35].

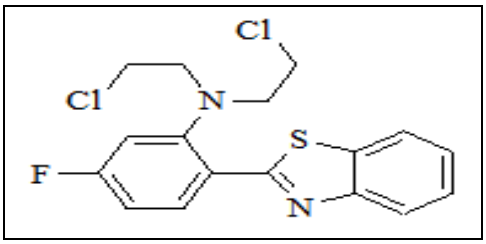


FIG. 16: STRUCTURE OF 2-(benzo[d]thiazol-2-yl)-N,N-bis(2-chloroethyl)-5-fluoroaniline

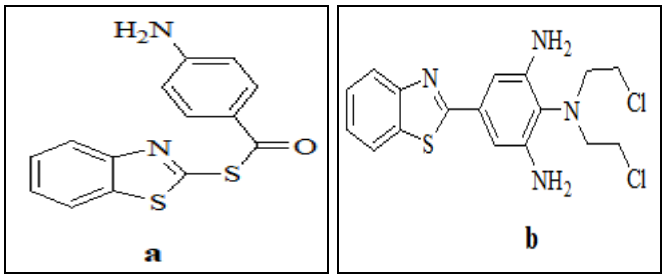


FIG. 17: a) *S*-benzo[*d*]thiazol-2-yl 4-aminobenzothioate b) *S*-(benzo[*d*]thiazol-2-yl)-N^2, N^2-bis(2-chloroethyl) benzene-1,2,3-triamine

Anti-Inflammatory: In 2015 Sadhasivam G *et al.*, synthesized some benzothiazole derivative **Fig. 18** and evaluated their anti-inflammatory activity. In their study, they found that compound *N*-(6-{[(4-cyclohexylphenyl) sulfonyl] amino}-1, 3-benzo thiazol-2-yl) acetamide possesses excellent activity. While compound *N*-(2-acetamido-1,3-benzothiazole -6-yl)-2-(1*H*-indol-3-yl) acetamide, *N*-(2-acetamido -1, 3-benzothiazol -6 -yl) -2 -(3 -fluorophenyl) acetamide, (2*E*)-*N*-(2-acetamido-1,3-benzothiazol-6-yl) -3 -(2 -furyl) acrylamide and *N*-(6-{[(3-methoxyphenyl) carbamoyl] amino}-1, 3-benzo thiazol-2-yl) acetamide possess optimum anti-inflammatory activity [36].

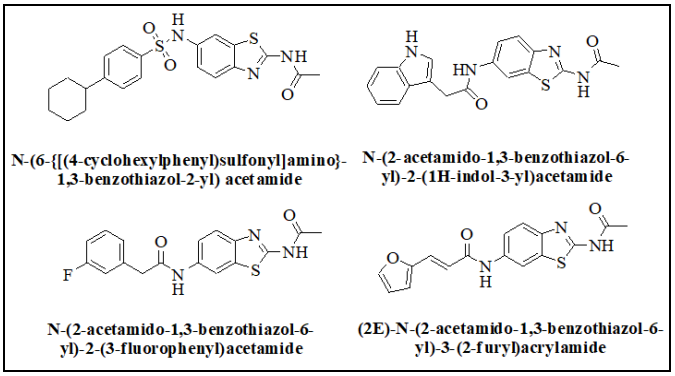


FIG. 18: STRUCTURE OF SADHASIVAM G *et al.*, SYNTHESIZED BENZOTHIAZOLE DERIVATIVE

In 2013 Kashinath DV *et al.* synthesized some pyrimido [2, 1-*b*] [1, 3] benzothiazole derivative and evaluated their anti-inflammatory activity. In their study they found that compound (4*R*) 2-amino-7-methoxy-4-(3, 4, 5-trimethoxyphenyl)-4*H*pyrimido [2, 1-*b*] [1, 3] Benzothiazole-3-carbonitrile, (4*R*) 2-amino-7-chloro-4-(4-chloro-phenyl)-4*H* pyrimido [2,1-*b*] [1, 3] benzothiazole-3-carbonitrile, and (4*R*) 2-amino-6-chloro-4-(4-chlorophenyl)- 4*H* pyrimido [2, 1-*b*] [1, 3] benzothiazole-3-Carbonitrile possess excellent anti-inflammatory activity [37].

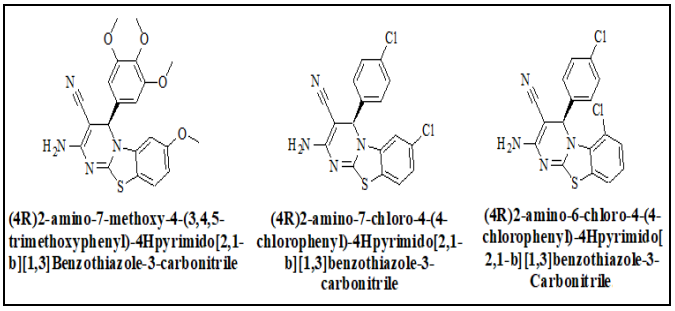
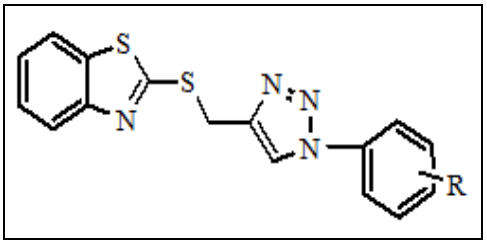


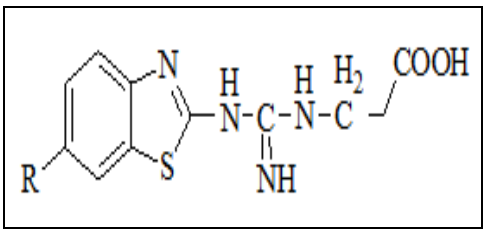
FIG. 19: STRUCTURE OF MOST POTENT BENZOTHIAZOLE DERIVATIVES

In 2014 Shafi *et al*. synthesized a series of 2-mercaptobenzothiazole and 1, 2, 3-triazoles **Fig 20**. The synthesized compounds have been tested for their anti-inflammatory activity by using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema. Among the tested compounds, compound 13d demonstrated a potent, selective COX-2 inhibition with COX-2/COX-1 ratio of 0.44. Compounds 13a, 13d, 13e, and 13f possess significant anti-inflammatory activity as compared to the standard drug Ibuprofen [38]. In 2009 Venkatesh P *et al.*, prepared a series of Substituted1, 3-benzothiazole-2-amine **Fig. 21** in which three compounds 12a (5-chloro-1, 3-benzothiazole-2-amine), 12b (6-methoxy-1, 3-benzothiazole-2-amine) and 12c (4-methoxy-1, 3-benzothiazole-2-amine) were found the most active compounds for anti-inflammatory activity [39].



Compound	R
a	o-Cl
d	p-F
e	p-Br
f	p-NO_2

FIG. 20: STRUCTURE OF 2[(substituted phenyl, 1, 2, 3 triazoles)methyl] thio benzothiazole



Compound	R
a	5-Cl
b	6-methoxy
c	4- methoxy

FIG. 21: STRUCTURE OF SUBSTITUTED 1, 3-benzothiazol-2-amine

In 2008 Gurupadayya B *et al*, synthesized azatidin-2-ones & thiazoline-4-ones encompassing benzothiazole derivatives **Fig. 22** and evaluated for anti-inflammatory activity using carrageenan-induced rat hind paw edema method. Diclofenac sodium used as standard drug [40].

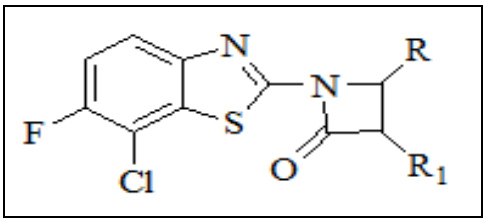


FIG. 22: STRUCTURE OF SUBSTITUTED azatidin-2-ones

In 2003 Parmshivappa R *et al.*, synthesized 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-230 **Fig. 23**. [5]

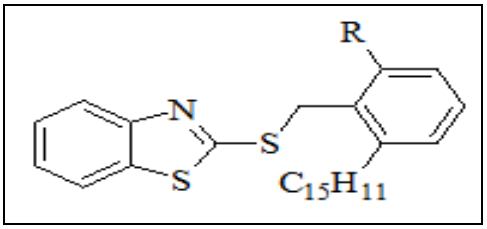
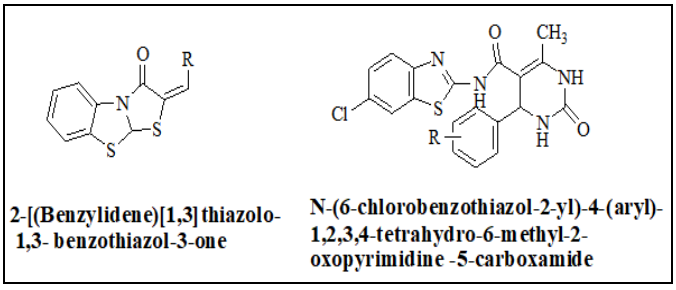


FIG. 23: STRUCTURE OF 2-[(2-alkoxy-6-pentadecyl phenyl) methyl] thio-1-Hbenzimidazoles / benzothiazole

Anticonvulsant Activity: In 2017 Siddiqui N *et al*., synthesized 2-[(6-substituted benzo[*d*]thiazol-2-ylcarbamoyl) methyl] -1-(4-substituted phenyl) isothiourea and evaluated their anticonvulsant activity. In their study, they found that all synthesized compound possess good anticonvulsant activity [44]. In another study of 2017 Raju GN *et al*., synthesized some benzothiazole derivative **Fig. 24** 2-Benzylidene [1,3] thiazole-1, 3-benzothiazole-3-ones (a, b) and N-(6-Chlorobenzothiazol-2-yl)-4-(aryl)-1, 2, 3, 4 -tetrahydro-6 -methyl- 2-oxopyrimidine-5-carboxamide (c, d) containing derivative posses good activity against convulsion [42].



a	R= m-$NO_2C_6H_4$	c	R= p-OH C_6H_4
b	R= p-$OCH_3C_6H_4$	d	R= p-$N(CH_3)_2$ C_6H_4

Fig. 24: RAJU GN *et al.*, SYNTHESIZED BENZO THIAZOLE DERIVATIVES

In 2016 Jin C *et al.*, synthesized benzothiazole derivatives **Fig. 25** and evaluated their anti-convulsant activity. In their study they found that compounds2-((1H-1,2,4-triazol-3-yl)thio)-N-(6-((3-fluorobenzyl) oxy) benzo [d] thiazol-2-yl) acetamide, and 2-((1H-1, 2, 4-triazol-3-yl) thio)-N-(6-((4-fluorobenzyl)oxy) benzo [d] thiazol-2-yl) acetmide are the most potent [43].

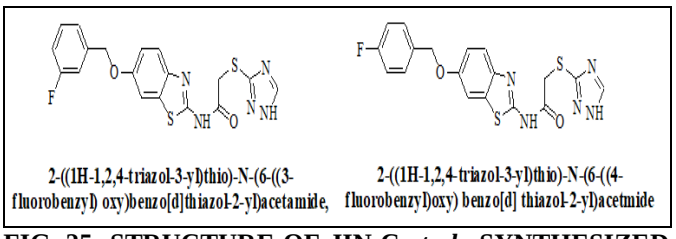
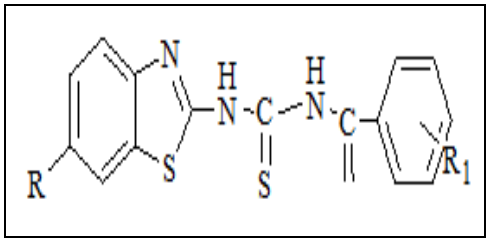


FIG. 25: STRUCTURE OF JIN C *et al.*, SYNTHESIZED BENZOTHIAZOLE DERIVATIVES



R	Br, Cl, F, NO_2, CH_3, OCH_3
R1	H, 2-Cl, 4-Cl, 4-OCH_3

FIG. 26: STRUCTURE OF SUBSTITUTED 1, 3-benzothiazole-2-yl benzamides

In 2007 Siddiqui N *et al.*, and Amnerkar N *et al.*, synthesized a series of N-(6-substituted-1, 3-benzothiazole-2-yl)-4- {[(substituted amino) carbo nothioyl] amino} benzene sulfonamides (x), prop-2-eneamido and 1-acetyl-pyrazoline derivatives of aminobenzothiazole (y) and found that most of the compounds were active as anticonvulsants in MES and PTZ induced seizures **Fig. 26**. [44, 45] In 1992 Jimonet P. *et al.* Synthesized a compound 2-(-4-aryl thiosemicarbazidocarbonylthio) benzo thiazoles **Fig. 27** which is anticonvulsive agents and show activity against phenyltetrazolone induced convulsions [46].

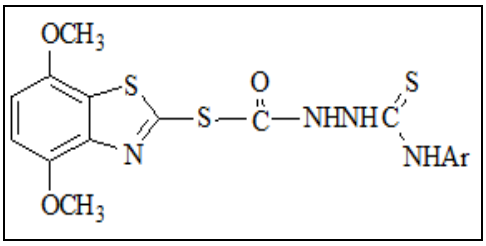
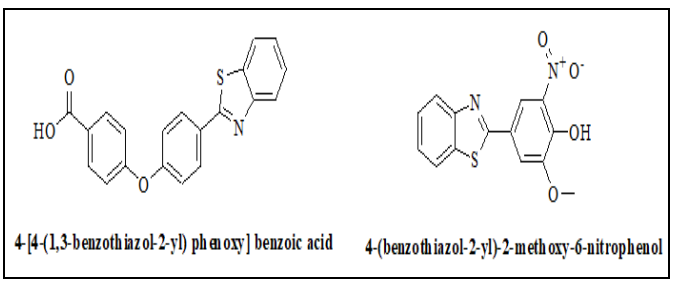


FIG. 27: STRUCTURE of 2-(-4- arylthiosemicarbazido carbonylthio) benzothiazoles

Antioxidant: In 2018 Amin S *et al*, synthesized 2 aryl substituted benzothiazole derivative **Fig. 28** and evaluated their antioxidant activity. In their study they found that compound 4-[4-(1, 3-benzothiazole-2-yl) phenoxy] benzoic acid, 4-(benzothiazole-2-yl)-2-methoxy-6-nitrophenol, 2-[2-(4-chlorobenzoyl) phenyl]-1, 3-benzothiazole and 4-(1,3-benzothiazole-2-yl)-2-ethoxyphenol possess antioxidant activity [47].



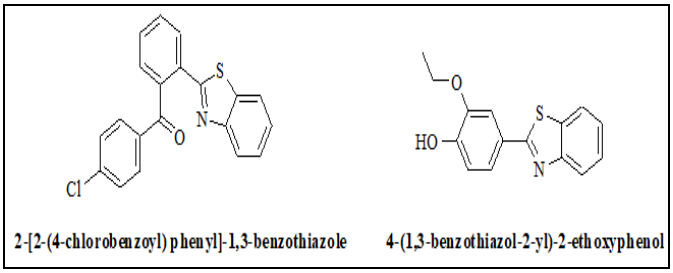


FIG. 28: STRUCTURE OF AMIN S *et al.*, SYNTHESIZED BENZOTHIAZOLE DERIVATIVE

In 2017 Starcevic K *et al.*, synthesized new amidino substituted benzothiazole derivatives **Fig. 29** and evaluated their antioxidant potency. In their study, they found that compound 6-Amidinium-2-(2, 3, 4-trihydroxyphenyl) benzothiazole chloride and 6-(4, 5-Dihydro-1H-imidazole-3-ium-2-yl)-2-(2, 3, 4-trihydroxyphenyl) benzothiazole chloride possess most potent antioxidant effect [48].

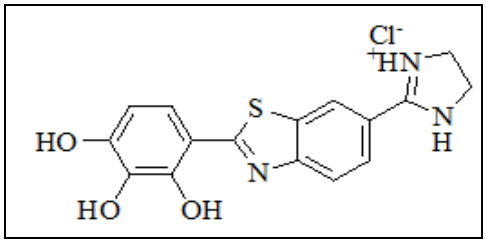


FIG. 29: STRUCTURE OF 6-(4, 5-Dihydro-1H-imidazole-3-ium-2-yl)-2-(2, 3, 4-trihydroxyphenyl) benzothiazole chloride

In 2016 Rosales-Hernandez MC *et al*, synthesized some benzothiazole derivatives **Fig. 30** and evaluated their antioxidant activity. In their study, they found that compound (E)-5-((benzo[d]thiazol-2-ylimino) (methyl this) methylamino)-2-hydroxybenzoic acid possess good antioxidant activity [49]. In 2010 Guzel *et al.*, synthesized a series of 3H-Spiro [1, 3-benzothiazole-2, 30-indol]-20(10H) - ones. The new compounds were screened for their antioxidant activities such as the Fe^{3+}ascorbate system induced inhibition of lipid peroxidation (LP) in liposomes, Trolox equivalent antioxidant capacity (TEAC), scavenging effect on diphenyl picryl hydrazine (DPPH), and reducing power. These compounds showed potent scavenging activities against DPPH and 2, 20-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS+) radicals, reducing powers, and strong inhibitory capacity on lipid peroxidation. Compound 20d incorporating methyl both at R1 and R2 was found to be the most potent anti-oxidant [50].

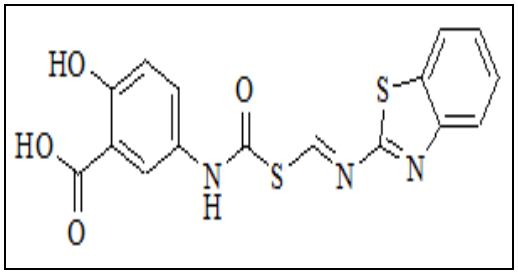


FIG. 30: STRUCTURE OF (E)-5-((benzo[d]thiazol-2-yl imino) (methyl this) methylamino)-2-hydroxybenzoic acid

In 2010 Karali *et al.*, synthesized 1', 5'-dimethyl-3H-spiro [benzo [d] thiazole-2, 3'-indolin]-2'-one and screened for their antioxidant activities. Among synthesized compounds, compound **Fig. 33** was found to be the most potent antioxidant [54]. In 2009 Rima *et al.*, synthesized **Fig. 34** a series of new compounds derived from benzothiazoles and thiadiazoles.

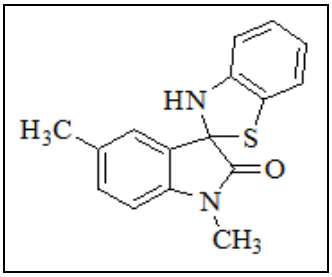


FIG. 31: STRUCTURE OF 1', 5'-dimethyl-3H-spiro [benzo[d]thiazole-2, 3'-indolin]-2'-one

In 2009 Cressier D *et al.*, Synthesized **Fig. 32** a series of new compounds derived from benzothiazoles and thiadiazoles. All the synthesized compounds were screened for anticonvulsant activity. The majority of these compounds were subjected to antioxidant activity screening by determining the DPPH or ABTS free radical scavenging using simple UV spectroscopic methods. These compounds have shown good activity. Among all the synthesized compound, compound 1,5-dimethyl-3H-spiro[benzo[d]thiazole -2,3-indolin]-2-one **Fig. 31** has shown a strong antioxidant activity [51].

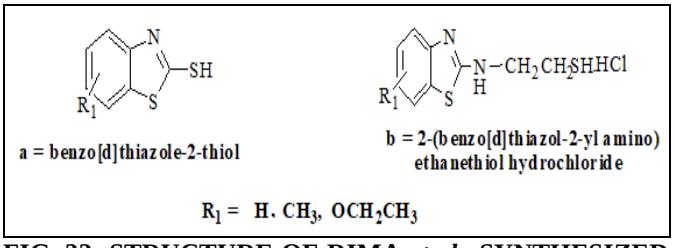


FIG. 32: STRUCTURE OF RIMA *et al.*, SYNTHESIZED BENZOTHIAZOLES DERIVATIVE

Anti-Diabetic Activity: In 2016 Kumar S *et al.*, synthesized some 2- ((benzothiazole-2 -ylthio) methyl)-5-phenyl-1, 3, 4 oxadiazoles and evaluated their anti-diabetic activity **Fig. 33**. In their study, they found that compounds 2-(((6-nitrobenzo [d]thiazol-2-yl) thio) methyl)-5-(4-nitrophenyl)-1, 3, 4-oxadiazole possess excellent anti-diabetic activity [52].

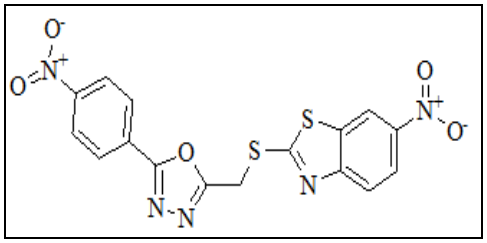


FIG. 33: STRUCTURE OF 2-(((6-nitrobenzo[d]thiazol-2-yl) thio) methyl)-5-(4-nitrophenyl)-1, 3, 4-oxadiazole

In 2013 Sasson S *et al.*, synthesized some benzothiazole derivative **Fig. 34** and evaluated their antidiabetic activity. In their study, they found that compound 2- (benzo[*d*] thiazol-2-ylmethyl thio)-6-ethoxybenzo[*d*] thiazole possesses good antidiabetic activity [53]. In 2012 Mariappan G *et al.*, synthesized some benzothiazole derivative **Fig. 35** and evaluated antidiabetic activity and in their study, they found that all synthesized compound possess prominent antidiabetic activity among all compounds, N-(6-chlorobenzoate [d] thiazol-2-yl)-2-morpholinoacetamide found to be most potent compound [54].

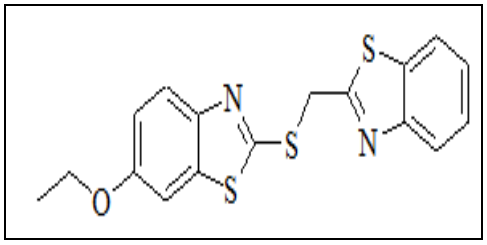


FIG. 34: STRUCTURE OF S2- (benzo[*d*] thiazol-2-ylmethylthio)-6-ethoxybenzo[*d*] thiazole

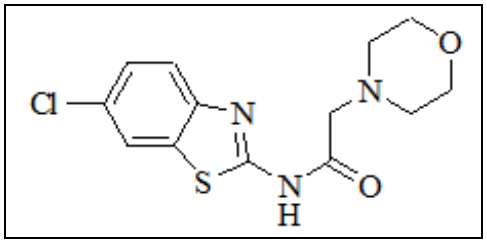


FIG. 35: STRUCTURE OF N-(6-chlorobenzo[d]thiazol-2-yl)-2-morpholinoacetamide

In 2005 Pattan S *et al.*, synthesized 2-amino[5` (4-sulphonyl benzylidine)-2, 4-thiazolidnedione]-7-chloro-6-flurobenzothiazole series and screened for their antidiabetic activity on Albino rat by Alloxan induced tail tipping method **Fig. 36**. [16]

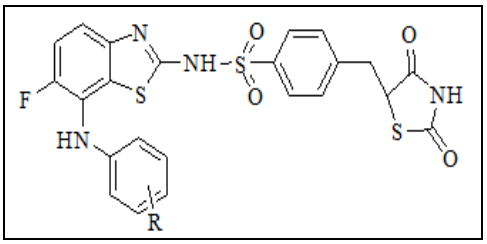


FIG. 36: STRUCTURE OF 4((2,4-dioxothiazolidin-5-yl)-N-(6-fluoro-7-(substituted phenylamino) benzo [d] thiazol-2-yl) benzenesulfonamide

In 2008 Nitta A *et al.*, synthesized a series of dipeptidyl peptidase inhibitor 40 IV for the treatment of type 2 diabetes and evaluated their activity. The compound (3R)-3-amino-4- (2, 4, 5-trifluoro phenyl) - N- {4- [6- (2- methoxy ethoxy) - benzothiazole- 2- yl] tetrahydropyran- 4- yl} butanamide **Fig. 37** was found to reduce the blood glucose level up to a significant extent in an oral glucose tolerance test [55, 56].

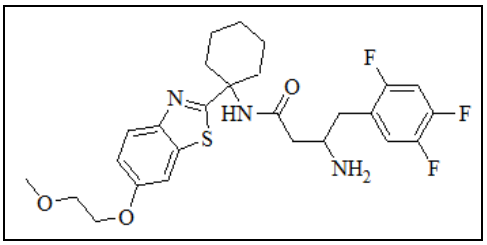


FIG. 37: STRUCTURE OF 3-amino-N-(1-(6-(2- methoxy ethoxy) benzo [d] thiazol-2-yl) cyclohexyl)-4-(2, 4, 5-trifluorophenyl)butanamide

In 2009 Paoli and co-workers prepared a small library of 2-aryl sulfonyl amino benzothiazoles and screened them for protein tyrosine phosphatase 1B inhibition. The most active compounds (a) (b) were observed rapidly reversible inhibitors of PTP-1B and significantly lowered plasma glucose concentration **Fig. 38**. [57]

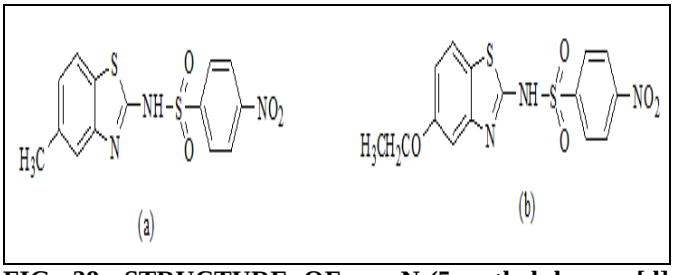


FIG. 38: STRUCTURE OF a= N-(5-methyl benzo [d] thiazol-2-yl)-4- nitrobenzenesulfonamide, b=N-(5-ethoxyl benzo [d] thiazol-2-yl)-4-nitrobenzenesulfonamide

Anthelmintic Activity: In 2015 Amnerkar N.D. *et al.*, synthesized some 4-(6-substituted-1, 3 benzothiazole-2-yl) amino-1, 3-thiazole-2-amines derivatives and evaluated their anthelmintic activity. In their study, they found that 4-(6-Ethoxy-1, 3-benzothiazole-2-yl) amino-2-(2-chlorophenyl- methylidene) amino-1, 3-thiazole possess good activity **Fig. 39**. [45]

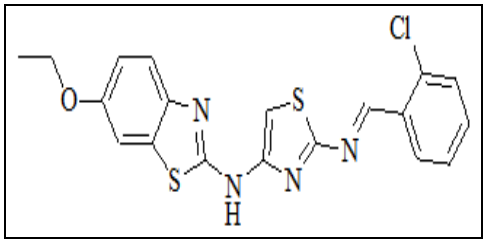


FIG. 39: STRUCTURE OF 4-(6-Ethoxy-1, 3-benzothiazole-2-yl) amino-2-(2-chlorophenyl-methylidene) amino-1, 3-thiazole

In 2011 Sathe BS *et al.*, synthesized fluoro benzothiazole derivative and evaluated their anthelmintic activity and in their study, they found that all compounds possess significant activity [64]. In 2011 Munirajasekhar *et al.*, synthesized a series of 6-substituted-2-hydrazino-1,3- benzothiazoles (28 a-e). All the synthesized compounds were evaluated for anthelmintic activity against *Eudrilus eugenie* A species and Megascoplexkonkanensis **Fig. 40**. [58, 59]

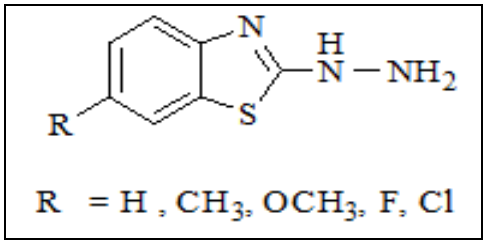


FIG. 40: STRUCTURE OF 6-substituted-2-hydrazino-1,3-benzothiazoles

In 2011 Suresh *et al.*, synthesized a series of 3-(2-hydrazino benzothiazoles) - substituted Indole-2-one. All the synthesized compounds were screened (x = a-f) and (y = a-f) for anthelmintic activity by using Indian adult earthworms *Pheretima posthuma*. The compounds d, f, and d have shown good paralytic time, compared to standard albendazole drug **Fig. 41**. [60] In 2009 Sreenivasam *et al.*, synthesized fluoro-benzothiazole comprising sulfonamide pyrazole derivatives. They screened and synthesized for anthelmintic activity by using earthworms *Peritum posthuma*. Albendazole was used as standard drug. The compounds were evaluated by the time taken for complete paralysis and death of worms **Fig. 42**. [61]

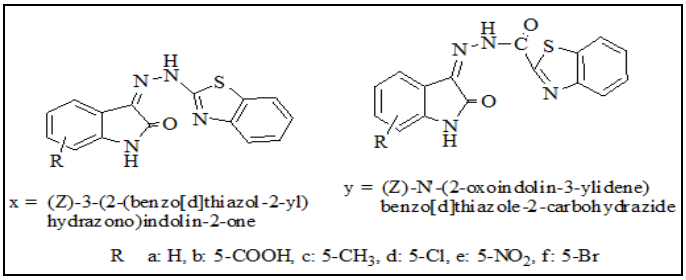


FIG. 41: SURESH *et al.*, (2011) SYNTHESIZED DERIVATIVES

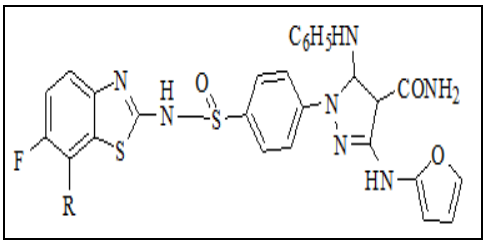


FIG. 42: STRUCTURE OF SULFONAMIDE PYRAZOLE DERIVATIVES

In 1998 Ghoneim KM *et al.*, synthesized an 8-fluoro-9-substituted benzothiazole (5, 1-b) -1, 3, 4-triazoles **Fig. 43**. Compounds were prepared and were studied for their anthelmintic activity44 against earthworm, *Pheretima posthuma*. A compound with R= o-nitro, aniline substituent was found to possess excellent anthelmintic activity than the other compounds; whereas all the other compounds are found to possess a low level of activity [62].

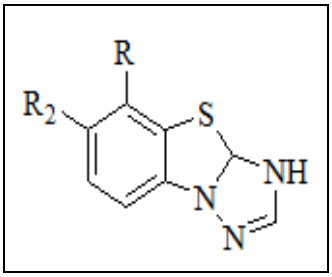


FIG. 43: STRUCTURE OF 8-fluoro-9-substituted benzo thiazole (5, 1-b) -1, 3, 4-triazoles

Antiviral Activity: In 2003 Nagarajan S *et al.*, synthesized compounds which are HIV-1 protease inhibition and it were observed with novel benzothiazole sulfonamides (a) and (b) with an IC_{50} value in the 2-3nM range. The carbamate analogs were found to be better antiviral and inhibitors of HIV-1 Protease **Fig. 44**. [63]

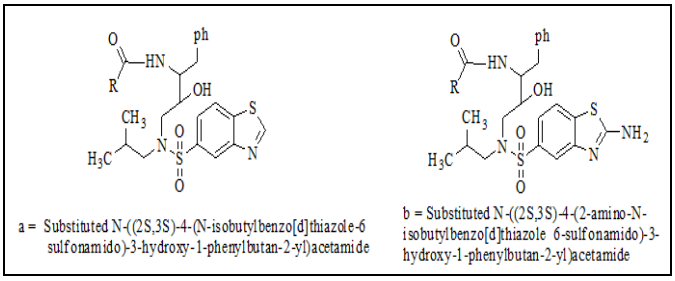


FIG. 44: STRUCTURE OF NAGARAJAN S *et al.*, SYNTHESIZEDBENZOTHIAZOLE DERIVATIVE

MTP Inhibition Activity: In 2009 Chi B *et al.*, synthesized triamide derivatives based on benzothiazole templet. A series of these compounds shown potent enterocyte-specific microsomal triglyceride transfer protein (MTP) inhibitors. Inhabitation of MTP by small molecules, therefore lead to a reduction in plasma triglyceride and cholesterol level **Fig. 45**. [64]

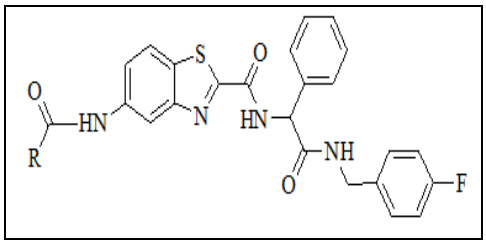


FIG. 45: STRUCTURE OF 5-substituted amido-N-(2-(4-fluorobenzylamino) -2 -oxo -1 phenylethyl) benzo [d] thiazole-2-carboxamide

Antimalarial Activity: In 2016 Sarkar S *et al.*, synthesized some benzothiazole derivative and evaluated their antimalarial activity. In their study, they found that compound (E)-4-((2-(benzo [d]thiazol-2-yl) hydrazono) methyl) benzene-1, 2-diolposses most potent activity **Fig. 46**. [65]

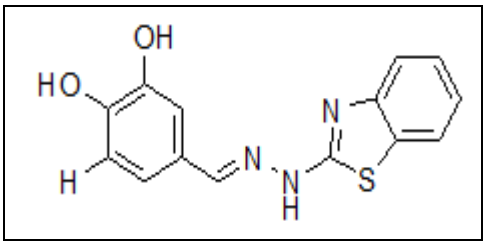


FIG. 46: STRUCTURE OF (E)-4-((2-(benzo[d]thiazol-2-yl) hydrazono) methyl) benzene-1, 2-diol

In 2007 Bowyer PW synthesized some benzothiazole derivative to inhibit N-myristoyl transferase of *Plasmodium falciparum*. In their study, they found that among all compounds, two compounds possess good antimalarial activity [66]. In 2004 Hout S *et al.*, synthesized compounds (a) and (b) as the antimalarial agents. 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 (a) and (b) as the antimalarial agents of clinical and biological research **Fig. 47**. [67]

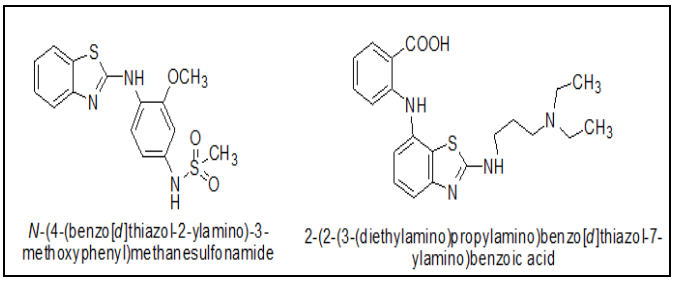


FIG. 47: STRUCTURE OF HOUT S *et al.* SYNTHESIZED BENZOTHIAZOLE DERIVATIVE

CONCLUSION: Based on the all research and review article we can say that it is a true statement that benzothiazole scaffold is a versatile and multifunctional molecule which possess therapeutic effect in various disease like cancer, diabetes, and others various marketed preparations of benzothiazole also available like neuroprotective drug (Riluzole), diuretic drug (Ethoxolamide), antiparkinson drug (Pramipexole) and Alzheimer's disease (Thioflavine). It would be significant for further research in the development of the better drug, representing successful matrix for the medicinal agent.

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CONFLICT OF INTEREST: The author declares no conflict of interest.

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